NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer (CDF Review of TA416) [ID1577]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer (CDF Review of TA416) [ID1577]

Contents:

The following documents are made available to consultees and commentators:

The final scope and final stakeholder list are available on the NICE website.

1. **Company submission** from AstraZeneca

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. EGFR Positive UK
   b. Joint submission from the Royal College of Physicians
   c. Public Health England Report commissioned by NHS England

4. **Expert personal perspectives** from:
   a. Dr Shobhit Baijal, Consultant Medical Oncologist – clinical expert, nominated by AstraZeneca
   b. Jenny Abbott – patient expert, nominated by EGFR Positive UK
   c. Professor Peter Clark – CDF clinical lead

5. **Evidence Review Group report** prepared by Liverpool Review and Implementation Group (LRiG)

6. **Evidence Review Group erratum** prepared by Liverpool Review and Implementation Group (LRiG)

7. **Technical Report**

8. **Technical engagement response** from AstraZeneca
   a. AstraZeneca main response
   b. AstraZeneca supplementary material

9. **Technical engagement responses from consultees and commentators:**
   a. Joint response from the Royal College of Physicians

10. **Evidence Review Group critique of company technical engagement response** prepared by Liverpool Review and Implementation Group (LRiG)

11. **Letter from AstraZeneca with updated price**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review of TA416

Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer [ID1577]

Company evidence submission for committee

June 2019

File name	Version	Contains confidential information	Date
		Yes/no	
CDF-review_TA416_Company submission_FINAL_redacted_3	3	Yes	18/12/19

Contents

Tables and figures

Cancer Drugs Fund review submission

A.1 Background

- Osimertinib is recommended as an option for use within the Cancer Drugs Fund for treating locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer in adults whose disease has progressed only:
    - after first-line treatment with an EGFR tyrosine kinase inhibitor and
    - if the conditions in the managed access agreement for osimertinib are followed.
- The committee noted that the key clinical-effectiveness evidence for osimertinib was taken from the AURA extension and AURA2 studies (FAD, 4.3). The committee was aware that overall-survival data were still immature and that a median overall-survival estimate was not calculable based on the available results (FAD, 4.4). The committee concluded that, because of the immaturity of the data, any estimate of an overall-survival gain for osimertinib compared with platinum-doublet chemotherapy was very uncertain and could have a very large effect on the ICER (FAD, 4.10).
    - Company's revised base-case ICER was £41,705 per QALY
    - Committee's preferred ICER was between, £60,663 per QALY using the generalised gamma extrapolation and the company's utility estimates, and £70,776 per QALY gained using the generalised gamma extrapolation and the ERG's alternative utility estimates
- The committee concluded that there was a plausibly cost effective range from £41,705 to £70,776 per QALY gained which provided the plausible potential for cost effectiveness.

A.2 Key committee assumptions

Area	Committee preferred assumptions
Population	• Adults with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC).
Comparators	• Platinum-doublet chemotherapy was the most relevant comparator for osimertinib in this appraisal
Generalisability	• The trials used as the basis for evaluating the efficacy of osimertinib in people with EGFR T790M mutation-positive NSCLC that has progressed on a previous TKI were broadly generalisable to clinical practice.
Overall survival	• Pooling the results for the 2 AURA trials was reasonable given that the studies were very similar regarding baseline characteristics. • The available data were too immature to robustly estimate the overall-survival advantage of osimertinib compared with platinum-doublet chemotherapy
Model structure	• The company's model structure is suitable for decision making
Extrapolation of overall survival	• Due to the immature data the company still had to extrapolate the overall-survival results from the clinical trials to the lifetime time horizon of the model. • The company used a Weibull distribution for the extrapolation of both osimertinib and platinum-doublet therapy which was not implausible. • The committee considered using a generalised gamma distribution a potentially more reasonable • There are several plausible overall survival extrapolation curves • Extrapolation of overall survival is unclear and requires further data collection
Utilities	• Company's base-case analysis were derived from EQ-5D-5L data collected in the AURA2 study and the modelled values were not treatment specific (that is, utility was 0.815 for progression-free disease and 0.678 for post-progression disease).

	• The ERG considered the utility values from the LUME-lung 1 study could be more reasonable (that is, 0.67 utility value for both the response and stable states and 0.64 for the progressed disease state. • The most plausible utility values fall somewhere between those used by the company and those suggested by the ERG.
Time-to-treatment discontinuation	• Time-to-treatment discontinuation had been included appropriately in the company's revised analysis.
End of life	• Evidence suggested that median overall survival was in the range of 20 months for people who had not had treatment before: about 15 months for people who have been previously treated with an EGFR TKI and have the T790M mutation. The short life expectancy criterion was met. • The committee considered that because of the immaturity of the data for osimertinib, any estimate of an overall-survival gain compared with platinum-doublet chemotherapy was very uncertain. • The committee concluded that osimertinib could plausibly meet the criteria to be considered a life-extending, end-of-life treatment. However, this should be reconsidered as more data become available.

A.3 Other agreed changes

- The FAD expressed some uncertainty in the most appropriate utilities that should be used. If further evidence is available, an exploration of the most appropriate utilities should be performed.

- The company should not alter the decision-problem, submit additional evidence or make further alterations to the model during the CDF review period unless NICE requests or agrees to this in advance.

A.4 The technology

Table 1 Technology being reviewed

UK approved name and brand name	Osimertinib (Tagrisso)
Mechanism of action	Highly selective and irreversible inhibition of activating sensitising EGFR mutation (EGFRm+) and activating resistance mutation T790M, without affecting the activity of wild type EGFR. Inhibition of phosphorylation of EGFR and downstream signalling leads to tumour growth inhibition and also induces cell cycle arrest.
Marketing authorisation/CE mark status	For osimertinib in locally advanced or metastatic EGFR mutation positive (Ex19del or L858R) NSCLC, the CHMP Opinion was sent to the European Commission on 26 April 2018, and EMA approval for a marketing authorisation was granted on 8 June 2018. Osimertinib was previously granted approval for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC on 17 December 2015.
Indications and any restriction(s) as described in the summary of product characteristics	Osimertinib is indicated for: • the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations • the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.
Method of administration and dosage	Osimertinib is available as 40 mg or 80 mg oral tablets. The recommended dose is osimertinib 80 mg once a day until disease progression or unacceptable toxicity.
Additional tests or investigations	When considering the use of osimertinib as a treatment for locally advanced or metastatic NSCLC, it is necessary that EGFR mutation status is determined. EGFR mutation status should be determined by a validated test method, using either tumour DNA derived from a tissue sample or circulating tumour DNA (ctDNA) obtained from a plasma sample.
List price and average cost of a course of treatment	The list price for 30 tablets (either 40 mg or 80 mg) is £5770.00. The total cost of treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC is approximately £95,200 per patient, based on list price and average treatment duration in the pivotal AURA2 study (16.5 months to treatment discontinuation or death).

	This does not take into account the patient access scheme described below.
Commercial arrangement (if applicable)	A confidential PAS has been agreed with NHS England
Date technology was recommended for use in the CDF	October 2016
Data collection end date	January 2019

A.5 Clinical effectiveness evidence

Four main data sources are presented in support of this review;

- AURA pooled (pooled analysis of AURA extension and AURA2 single-arm studies of osimertinib 80mg)
- AURA3 (Phase3 randomised controlled trial comparing osimertinib 80mg with PDC)
- Data from SACT (PHE)
- Data collected by CDF from SACT

Table 2 Primary source of clinical effectiveness evidence

Study title	**AURA pooled**	**AURA3**	**SACT data cohort study**	**SACT data cohort study**
Study design	Single-arm study	Open-label RCT	SACT data cohort study	SACT data cohort study
Population	Patients with a confirmed diagnosis of advanced or metastatic (Stage IIIB-IV) EGFR T790M NSCLC, who have progressed following prior therapy with an approved EGFR TKI agent		Patients with a confirmed diagnosis of advanced or metastatic (Stage IIIB-IV) NSCLC, who have progressed following prior therapy with an approved EGFR TKI agent.	Patients receiving osimertinib for treating metastatic EGFRm T790M mutation-positive NSCLC in the Cancer Drugs Fund
Intervention(s)	Osimertinib	Osimertinib	Undefined Mixture of untreated and treated patients (approx. 2:1)	Osimertinib
Comparator(s)	Not applicable	Pemetrexed/paclitaxel chemotherapy (platinum-based doublet chemotherapy; PDC)	Not applicable	Not applicable
Outcomes collected that address committee's key uncertainties	**Overall survival (DCO5 – May 2018)**	Progression-free survival (PFS) Time to treatment discontinuation (TDT) Overall survival (OS)	Overall survival from the end of a patient's treatment with an approved EGFR-TKI agent (afatinib, erlotinib or gefitinib) Baseline characteristics in UK clinical practice	Treatment duration for the use of osimertinib Overall survival from the start of a patient's first treatment with osimertinib Baseline characteristics in UK clinical practice
Reference to section in appendix	Appendix 1 Appendix 7	Appendix 2 Appendix 6 Appendix 8	Appendix 3	Appendix 4 Appendix 5

Outcomes informing the base case economic model are indicated in bold. Outcomes not in bold are used in exploratory analyses to support the appraisal.

A.6 Key results of the data collection

A.6.1 *Overall survival*

AURA pooled

Both AURAext and AURA2 studies were prospectively designed to provide replication of the data: both had almost identical designs

The rationale for pooling data from AURAext and AURA2 is based on both studies having very similar designs in terms of patient population, study conduct, dose and formulation and outcome measures. They also included a well-defined, molecularly characterised patient population ensuring that all patients were confirmed as T790M positive based on central testing.

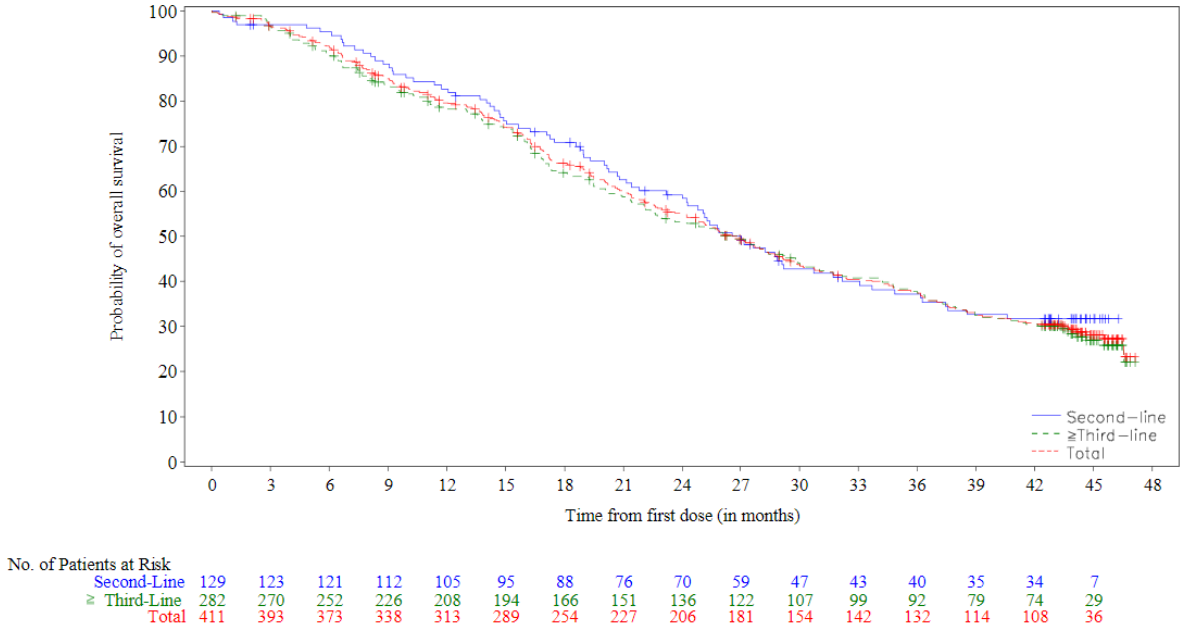
In the original submission (Appendix 2, Company response to ACD), the median OS wasn't reached (data maturity at DCO3 was <20% in AURAext/2) and the expected median OS for these patients based on the Weibull distribution for osimertinib in patients receiving osimertinib as 2L therapy was 40.15 months (versus 19.15 months for PDC).

It is noted that at the time of the original appraisal, there was evidence that the second-line population had better survival outcomes compared with later-line populations (TA416. Sections 4.4 & 4.9). The median survival (Table 3) and Kaplan Meier plot (Figure 1) for patients according to the line of treatment (i.e. 2nd-line vs. 3rd-line +) at DCO5 do not deviate significantly from the pooled population (Appendix 1).

Table 3: Median overall survival by treatment cohort

	Second-line (N=129)	≥ Third-line (N=282)	Pooled data (N=411)
Total number of deaths	82	189	271
Median Overall survival (months)	26.5	26.8	26.3
95% CI for Median overall survival	24.02, 31.74	22.14, 29.93	24.02, 29.14
Median follow-up for overall survival (months)	25.1	22.7	24.0

Figure 1: Overall Survival - by line of treatment (2nd or ≥3rd line) and total, Kaplan-Meier plot



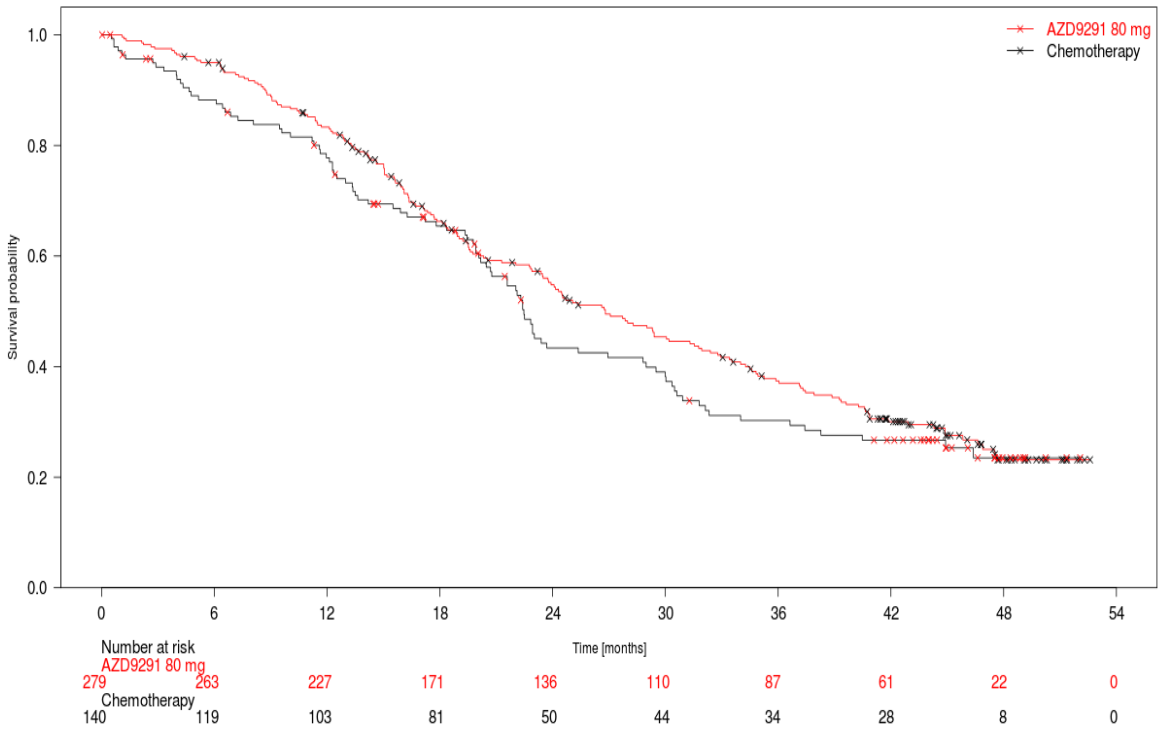
AURA3

The AURA3 study was a randomised, international, open-label phase 3 trial in which 419 patients with T790M-positive EGFRm NSCLC, who had disease progression after treatment with first-line EGFR-TKI, were randomised 2:1 to receive either osimertinib 80mg once daily until progression or platinum-based doublet chemotherapy (PDC) every 3 weeks for up to 6 cycles (18 weeks maximum). A total of 419 patients were screened and randomised to the two treatment arms between August 2014 and September 2015. The results of the mature OS analysis, which were not available at the time of the original appraisal, are presented in Table 4 and Figure 2. It is important to note that patients randomised to chemotherapy in AURA3 were permitted to switch treatments after disease progression and 71% of patients received osimertinib in this way (Appendix 2 and 6).

Table 4: Median overall survival in AURA3 (DCO4)

	Osimertinib 80mg (N=279)	**Chemotherapy (N=140)**
Total number of deaths	188 (67.4%)	93 (66.4%)
Median Overall survival (95% CI)	26.8 (23.49, 31.54)	22.5 (20.17, 28.81)
Median follow-up for overall survival in all patients (months)	23.5	20.3
Median follow-up for overall survival in censored patients (months)	42.7	43.2
Hazard Ratio (95% CI)	0.87 (0.67, 1.13)	
2-sided p-value	0.277	

Figure 2: Overall survival (AURA3 DCO4), KM plot (unadjusted for crossover)

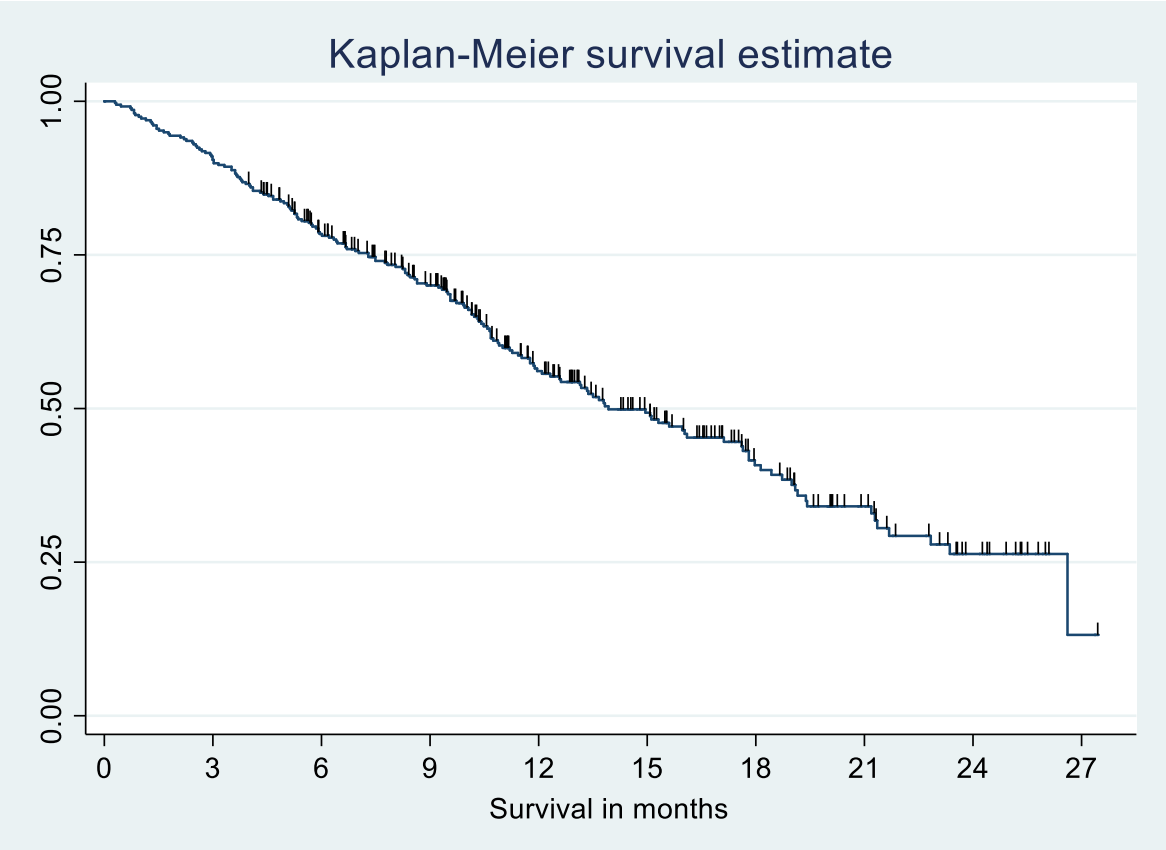


CDF/SACT datasets

Overall survival data was collected by the CDF for patients receiving osimertinib from October 2016 until January 2019 (N=357. Appendix 3).

Figure 3 provides the Kaplan-Meier curve for overall survival, censored at 15 January 2019 (maximum follow-up period for survival was 28 months). The median survival was 13.9 months [95% CI: 12.1, 17.6] (N=357). Survival at six months was 78% [95% CI: 74%, 82%] and 12-month survival was 56% [95% CI: 50%, 62%].

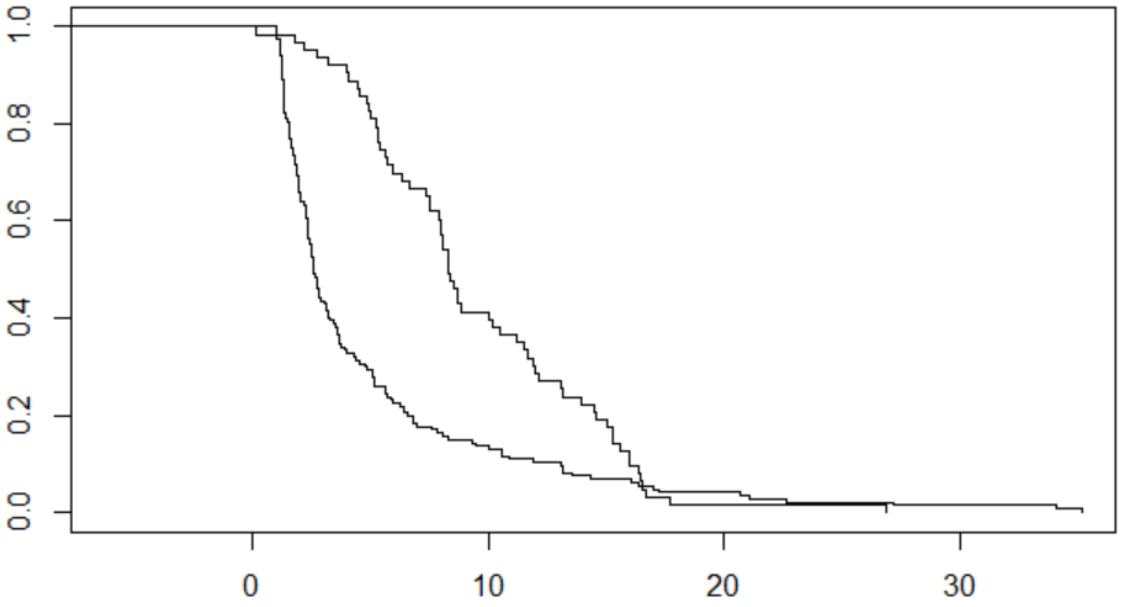
Figure 3: Kaplan-Meier survival plot for patients receiving osimertinib in the CDF (N=357)



The observed survival for patients receiving osimertinib in the CDF should be considered in the wider context of expected survival for these patients within the broader NHS. Unfortunately, survival outcomes for patients who have progressed after treatment with 1st-/2nd-generation TKI's (i.e. afatinib, erlotinib or gefitinib) were not collected as part of the data collection agreement with the CDF. To address this data gap, the cohort of patients identified from the SACT dataset (Appendix 4 and 5) and described in the appraisal of osimertinib in the first-line setting [ID1312], was re-interrogated to estimate the survival of patients from the time they stop treatment with 1st-/2nd-generation TKI's (i.e. afatinib, erlotinib or gefitinib).

The survival of patients, with Performance Status 0/1 who received any subsequent anticancer treatment after stopping initial treatment with a TKI, was 8.31 months (95% CI; 7.92, 11.17. N=68). For patients who did not receive any further treatment (but who were still alive 28 days after their last dose of TKI), median survival was only 2.56 months (95% CI; 2.33, 3.19. N=147).

Figure 4: Survival of patients in SACT diagnosed 2014/15 measured from the time they stop receiving 1L TKI.



Summary

There are a number of sources for the overall survival of patients receiving osimertinib in T790M positive EGFRm NSCLC; each associated with strengths and weaknesses which should be considered appropriately when interpreting the results.

Survival outcomes for patients treated with osimertinib in the 2L setting in the AURAext/2 and AURA3 studies were consistent and were approximately 26.5 months. In comparison, patients randomised to PDC in AURA3 survived for a median of 22.5 months, although more than 70% of these patients crossed-over to receive osimertinib in 3L. **Thus, in a randomised controlled trial setting, where the use of osimertinib in later lines is common, incremental median OS for patients treated with osimertinib in second-line is approximately** 4 **months.** The methods and results of the statistical adjustment for crossover are presented in Appendix 8 and summarised in Section A7.2.

In contrast, CDF data has shown that patients who received osimertinib in second-line had a median survival of 13.9 months – approximately half the survival of patients in the AURA studies. This observation must be considered in the context of the current background survival for such patients receiving standard of care in the NHS at this time. Analysis of data from Public Health England suggests that approximately one third of patients stopping treatment with an EGFR-TKI (for any reason including progression or tolerability) go on to receive a 2L treatment and have a median survival of approximately 8.3 months. For the remainder of patients who do not receive any further anticancer treatment, the outlook is much worse - median OS is less than 3 months. **Thus, the incremental median OS gain for patients treated in the NHS with osimertinib is between** 10.9 **and** 5.6 **months.**

Table 5: Summary of Overall survival outcomes for patients after progression on 1st-/2nd-generation TKI's

Source	**AURAext/2 (2nd line)**	**AURA3**	**CDF SACT**	**Non-CDF SACT**
Confirmed T790M EGFRm	Yes	Yes	Yes	No (assumed EGFRm based on 1L TKI treatment)
N (osimertinib)	129	279	357	N/A
mOS (95% CI)	26.5 (24.02, 31.74)	26.8 (23.49, 31.54)	13.9 (12.1, 17.6)	N/A
N (PDC)	N/A	140	N/A	68
mOS (95% CI)	N/A	22.5 (20.17, 28,81)	N/A	8.31 (7.92, 11.17)
N (No treatment)	N/A	N/A	N/A	147
mOS (95% CI)	N/A	N/A	N/A	2.56 (2.33, 3.19)
Notes		71% of patients randomised to PDC switched to osimertinib after confirmed progression.		Unknown T790M status. Significant rates of no subsequent treatment after 1L TKI.

A.6.2 *Progression-free survival*

AURA pooled

Updated progression-free survival outcomes from the pooled analysis of AURAext and AURA2 are used only in the MAIC (described in Appendix 7 and summarised in Section A7.1) and are not presented separately here.

AURA3

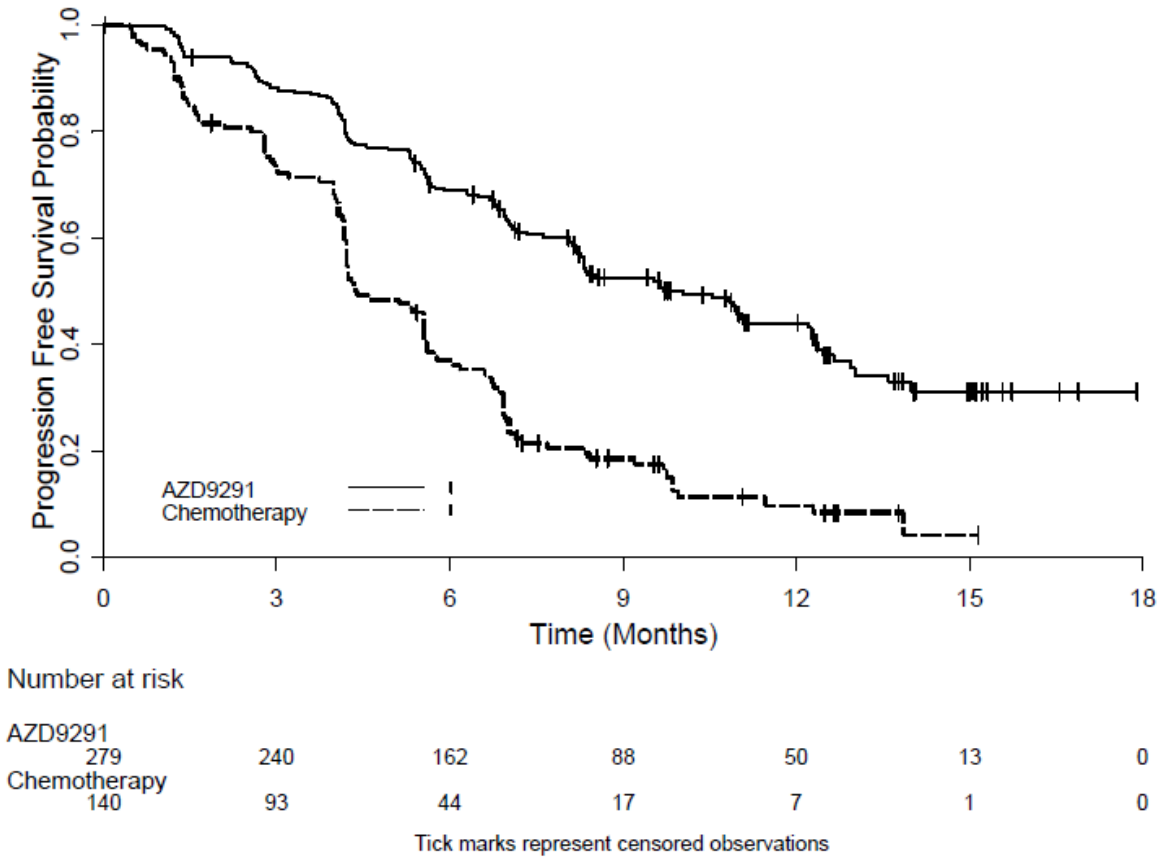
The PFS data was sourced from the AURA3 data cut-off on 15th April 2016 (DCO1. Appendix 6. Mok et al., N Engl J Med 2017; 376:629-640). A summary of the non-parametric data for PFS from AURA3 is presented below in Table 6 and the Kaplan-Meier curve in Figure 5.

Table 6 PFS summary data

	Osimertinib (n=279)	**PDC (n=140)**
Total events (%)	140 (50.2%)	110 (78.6%)
Median, months (95% CI)	10.1 (8.3, 12.3)	4.4 (4.2, 5.3)

PFS: progression-free survival; PDC: platinum-doublet chemotherapy

Figure 5: Progression-free survival (AURA3 DCO1) by investigators assessment, KM plot (FAS)



CDF/SACT datasets

Progression-free survival outcomes are not available from the SACT datasets.

A.7 Evidence synthesis

A.7.1 *Adjusted indirect comparison of osimertinib compared with platinum doublet chemotherapy*

In the original submission as part of TA416, the treatment effect of osimertinib monotherapy compared with platinum doublet chemotherapy was assessed using a match-adjusted indirect comparison (MAIC) of the pooled dataset of the AURAext/2 studies (N=411) and the chemotherapy arm of the IMPRESS study with a confirmed T790M mutation (N=61), respectively. As part of the response to ACD, the population of interest was based on the second-line treatment cohort from the AURAext/2 pooled dataset (n=129) and the IMPRESS T790M cohort (n=61). This remains the population of interest for the updated analysis based on AURAext/2 DCO4 (PFS DCO4; 1st November 2016) and DCO5 presented here (OS DCO5; 1st May 2018). Following cohort balancing, overlap and trimming, the final cohort of patients used in the analysis contained 92 patients treated with osimertinib (from AURAext/2) and 53 patients treated with PDC (from IMPRESS).

Progression Free Survival

An updated analysis of PFS for patients treated with osimertinib or platinum-based doublet chemotherapy (PDC) as a second-line treatment by a Cox proportional hazards model is presented in Table 7 based on the BICR and the T790M+adj set.

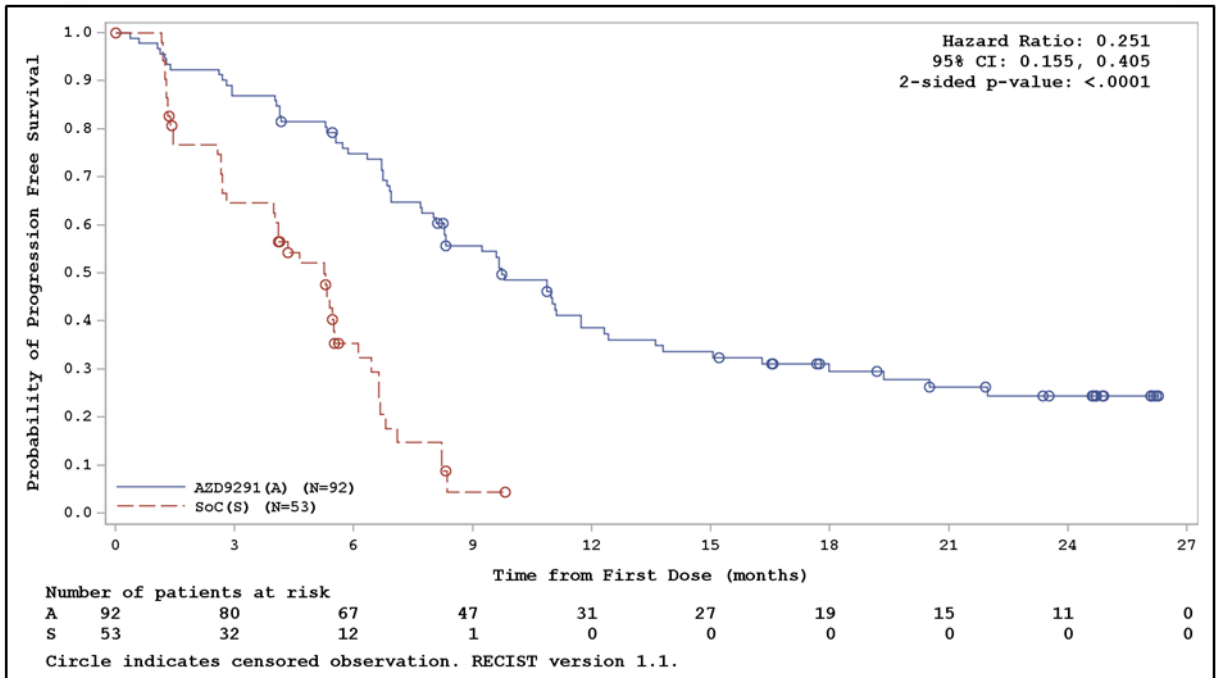
The PFS HR for second-line treatment based on ICR data demonstrated a statistically significant improvement for the osimertinib group relative to the platinum-based doublet chemotherapy group (HR 0.251, 95% CI 0.155 to 0.405, p-value <0.0001). Median PFS was 9.7 months for the osimertinib group compared with 5.3 months in the matched platinum doublet chemotherapy cohort. A KM plot for the primary calculated RECIST-defined PFS is presented in Figure 6. These data indicate that the treatment effect associated with osimertinib is consistent over time. Analyses of subgroups demonstrated that only EGFR mutation status produced significant interaction.

Table 7: Summary of Analysis of Progression-Free Survival by Independent Central Review for Second-Line Treatment (T790M+adj Set)

Treatment	N	Patients with events, n (%)	Median PFS (months)	Treatment effect (osimertinib vs PDC)		
				HR	95% CI	Two-sided p-value
Osimertinib	92	64 (69.6)	9.7	0.251	0.155, 0.405	<.0001
PDC	53	41 (77.4)	5.3			

PDC, Platinum-based doublet chemotherapy; PFS, Progression-Free Survival
The analysis was performed using a Cox proportional hazards model with treatment, subgroup, subgroup-by-treatment as factors and estimated PS as a covariate for each subgroup. HR <1 favours osimertinib. Progression includes death in the absence of RECIST progression.

Figure 6:Kaplan–Meier Plot of Progression-Free Survival by Independent Central Review for Second-Line Treatment



A, osimertinib; S, SoC / platinum-based doublet chemotherapy

Overall Survival

An updated analysis of OS by Cox proportional hazards model was performed at DCO5 for AURAext/2 and at DCO2 for IMPRESS for the T790M+adj set for patients given second-line treatment; the results are presented in Table 8.

Median OS time for the osimertinib group was [redacted] and the median OS time for the platinum-based doublet chemotherapy group was

14.1 months. The HR for OS for osimertinib relative to platinum-based doublet chemotherapy was [redacted]

Table 8: Analysis of Overall Survival for Second Line Treatment (T790M+adj Set)

		Patients with events, n (%)	Median OS (months)	Treatment effect (osimertinib vs PDC)		
Treatment	N			HR	95% CI	Two-sided p-value
Osimertinib	92	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC	53	[redacted]	14.1			

PDC, Platinum-based doublet chemotherapy
The analysis was performed using a Cox proportional hazards model with treatment as a factor and estimated PS as a covariate. HR <1 favours osimertinib.

A Kaplan–Meier plot for Overall Survival for patients given second-line treatment is presented in Figure 7. The Kaplan–Meier curves for the two treatment groups demonstrates the treatment effect over time with a separation of the curves after approximately 8 months of treatment, which is maintained and in favour of osimertinib.

Analysis of OS by subgroup was performed for patients treated at 2nd line. Analysis was only conducted if, for each subgroup level, there were at least 20 events combined for both treatments and at least five events in each individual treatment. The analysis demonstrated no significant interactions in any subgroups.

Figure 7: Kaplan–Meier Plot of Overall Survival for Second-Line Treatment (T790M+adj Set)

A.7.2 *Adjusting overall survival for treatment switching in AURA3*

The AURA3 trial protocol allowed patients randomised to chemotherapy to switch to osimertinib following confirmed disease progression. Overall, 99 of the 140 chemotherapy patients (71%) had crossed over at the final data cut-off for overall survival (DCO4; March 2019). Since osimertinib is not currently approved in the NHS for use as a later-line therapy, treatment switching does not represent current clinical practice. Therefore, the hazard ratio (HR) from the primary analysis in the intention-to-treat (ITT) population of AURA3 (0.87 [95% CI: 0.67, 1.13]) is likely to underestimate the overall survival (OS) benefit of osimertinib versus chemotherapy. and an estimate of OS for chemotherapy in the absence of switching to osimertinib is required.

Several potential statistical methods are available for adjusting overall survival to remove the effect of treatment switching, and a full description of the rationale for choosing the method selected here is available in Appendix 8. The results of that adjustment are summarised here.

Table 9 Overall survival hazard ratios and medians for osimertinib versus chemotherapy, adjusted using RPSFTM to remove the effect of switching

Method	**Treatment effect duration**	**Recensoring approach**	**OS Events – Osimertinib (n/N)**	**OS Events – PDC (n/N)**	**HR (95% CI), Cox model**	**HR (95% CI), Log rank**	**Median OS months Osimertinib (95% CI)**	**Median OS months PDC (95% CI)**
ITT Analysis	N/A	N/A	188/279	93/140	0.87 (0.68, 1.12)	0.87 (0.67, 1.12)	26.8m (23.5, 31.5)	22.5m (20.2, 28.8)
Base Case								
RPSFTM	On treatment	AF only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis								
RPSFTM	On treatment	Full	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RPSFTM	On treatment	None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RPSFTM	Treatment group	AF only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RPSFTM	Treatment group	Full	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RPSFTM	Treatment group	None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

p=0.2772 for all Cox analyses, p=0.2642 for all log rank analyses.
AF=Acceleration factor. HR=Hazard ratio. OS=Overall survival. NR=Not Reached. RPSFTM=Rank Preserving Structural Failure Time Model

Figure 8 Kaplan-Meier curve for base case switch-adjusted overall survival (RPSFTM, on-treatment approach, re-censoring for AF only)

The OS benefit of osimertinib increased in all RPSFTM switch-adjusted analyses compared to the ITT result. In the base case (RPSFTM, on-treatment approach, recensoring for AF), the switch-adjusted OS HR was [redacted] compared to 0.87 (95% CI: 0.67, 1.13) before adjustment. In sensitivity analyses using differing treatment effect durations and re-censoring approaches, the HR ranged from [redacted].

A.8 Incorporating collected data into the model

During the NICE technology appraisal for osimertinib in locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer (TA416), the committee noted that the overall-survival data for osimertinib taken from the AURA extension and AURA2 studies (November 2015; DC03) were still immature and median overall-survival estimate was not calculable based on the available results (FAD, 4.4). The committee concluded that, because of the immaturity of the data, any estimate of an overall-survival gain for osimertinib compared with platinum-doublet chemotherapy was very uncertain and could have a large effect on the ICER (FAD, 4.10).

In order to address the key uncertainty identified by the Committee as described in the FAD, AstraZeneca has updated the original cost-effectiveness model in line with the terms of engagement for CDF review. The decision problem and the model structure are identical to that previously submitted, however, the clinical efficacy data for OS for the osimertinib arm has been updated with the latest available data from AURAext/2 (May 2018; DCO5).

Additionally, during the CDF collection period the results from AURA3 (an open label RCT consisting of patients whose disease has progressed following treatment with an EGFR TKI) have become available. Therefore, PFS, OS and TDT data (and the related parametric extrapolations) from this additional source were also incorporated in the original cost-effectiveness model.

In summary, the original model was updated with the new evidence that became available during the CDF data collection period: two separate cost-effectiveness models are presented in the sections below, both built on the back of the original model submitted during the TA416, and incorporating the following changes:

Model a) NICE's accepted cost-effectiveness model and assumptions with **updated OS data for osimertinib from AURAext/2** (May 2018; DCO5) and related extrapolations

Model b) NICE's accepted cost-effectiveness model and assumptions with **OS, PFS and TDT for osimertinib and PDC from AURA3** (March 2019; DC04) and related extrapolations

This section summarises how clinical data collected during the CDF data collection period is incorporated into the economic model including a summary of the key modifications made to address concerns raised in the ACD. Finally, updated base case results and sensitivity analyses are described alongside a number of scenario analyses.

A.8.1 *Model a: overall survival from AURAext/2*

Non-parametric analysis

OS survival data were derived from the latest data cut (May 2018; DC05) from the pooled AURA extension and AURA2 studies (described above) and the IMPRESS

study (as per original analysis). At the time of DC05 OS data was 60.8% mature, with median OS of 24.84 months. The non-parametric analysis for OS is described in Table 10.

For PDC, OS data were sourced from the November 2015 data cut of IMPRESS (same data cut as described in the original appraisal). From the 132 patients included in the IMPRESS PDC arm, 61 were EGFR+ and T790M+ and included in the analysis. OS data were 72% mature, as shown in Table 10.

Table 10 Osimertinib OS non-parametric data

Outcome		**AURA pooled**	**IMPRESS T790M mutation positive**
Indication		Second-line	Second-line
Treatment		Osimertinib	Platinum doublet chemotherapy
Number of patients		92	61
OS	Total number of events	56 (60.8%)	44 (72%)
	Median months (95% CI)	28.75 (24.84-36.17)	14.1 (11.0-20.5)

OS = overall survival; CI = Confidence interval

Parametric survival models

The following section describes the updated parametric survival analysis performed on the latest data cut from the AURA pooled study. Standard guidance for fitting and selecting survival functions was used.

The analysis uses independent survival models for osimertinib and PDC. As the uncertainty highlighted by the NICE committee is related to the prediction of OS for osimertinib and given that new data are not available from the IMPRESS study, the section below only presents the curve selection for the osimertinib arm (the parametric model for PDC is the same as that preferred by the NICE committee during the original appraisal). Standard parametric models (exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised Gamma) were fitted to OS data, and visual inspection and statistical goodness-of-fit were performed in order to select the most appropriate extrapolation.

The fitted models resulting from the adjusted indirect comparison (Section A7.1) and the observed data from AURAext/2 are presented in Figure 9. Table 11 presents the mean, median, landmark rates and statistical fit of each models.

Figure 9: Osimertinib OS data (AURApooled, DCO5) and extrapolations

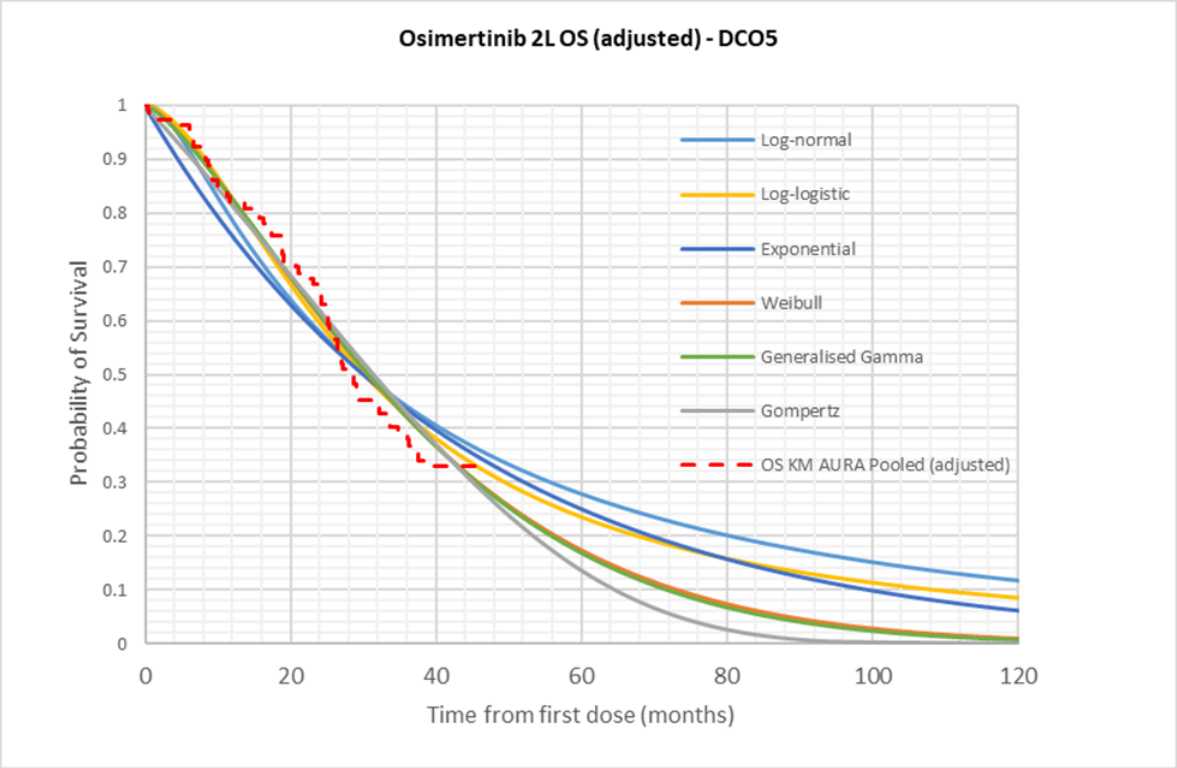


Table 11 Osimertinib predicted mean median, landmarks rates and statistical fit (OS, AURA pooled DC05, adjusted analysis)

			% Alive at				
Distribution	**Mean (months)**	**Median (months)**	**1 year**	**5 years**	**10 years**	**AIC (#)**	**BIC (#)**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	579.168	581.689
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	574.193	579.237
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	575.905	580.948
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	575.273	580.317
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	584.813	589.857
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	576.157	583.723

The visual inspection of the OS curves for osimertinib (Figure 9) shows that all curves tend to underestimate the survival up to 25 months, especially exponential and log-normal. The trend inverts after 25 months where some curves (log-normal; Log-logistic and exponential) overestimate the tail of the OS KM. The choice between the remaining distributions is less clear, but the Weibull distribution was selected for the base case analysis as it had the best statistical fit (AIC and BiC) and it also provides a relevant comparison with the analysis previously conducted on the DCO3 data.

A.8.2 ***Model b: survival analysis from AURA3***

Overall method of modelling survival

The primary data source for the cost-effectiveness model was the data from the AURA3 study. The follow-up period in AURA3 was shorter than the model time horizon, and extrapolation was required such that survival data could be usefully incorporated in the model. The survival analysis of PFS, OS and TDT was conducted using the approach outlined in the Technical Support Document for survival analysis published by the NICE Decision Support Unit. Following the selection of model type, in the presence of incomplete survival data, the most plausible parametric models are selected based upon statistical and visual fit to the observed data and the clinical plausibility of the extrapolation

Modelling progression-free survival

The log cumulative hazard plot (Appendix 9) indicates little evidence of non-proportional hazards since lines on the plot are generally parallel and there is no crossing. This suggests the use of a joint model with a treatment coefficient is appropriate for the AURA3 PFS data. All joint parametric survival models visual fits (presented in Appendix 9) and statistical fits (presented in Appendix 9) to the observed data are discussed alongside the plausibility of the extrapolations.

The visual inspection of the PFS curves for osimertinib shows that all curves have a similar fit up to 11 months where ~50% patients have progressed. Beyond this point several distributions were discarded on the basis of over- or under-estimation of PFS at longer timepoints. Therefore, the Weibull and generalised gamma represent the most plausible parametric models for osimertinib PFS. For PDC, given the high level

of data maturity the models with the best statistical goodness-of-fit corresponded to those with the best visual fit. Similar to the conclusions for osimertinib, the Weibull and generalised gamma were judged to represent the most plausible parametric models for PFS in these patients.

Given the visual and statistical fit and extrapolations discussed above the Weibull and generalised gamma are the most plausible parametric models for the AURA3 PFS joint analysis. However, Weibull is used in as the base case model given that:

- There is no evidence showing that the proportional hazards assumption does not hold, supporting the use of the joint model
- There is no evidence that the Weibull assumption does not hold (given that the lines are relatively straight excluding the initial stages on the hazard plot).

Modelling overall survival

The log cumulative hazard plot for OS adjusted for crossover (as described in Section A7.2) is shown in Appendix 9 and indicates little evidence of non-proportional hazards. Given the high maturity of the data (~70%), the AIC and BIC values, alongside visual inspection, provide a reliable evidence of model fit. This suggests the use of a joint model with a treatment coefficient is appropriate for the crossover adjusted AURA3 OS data. All joint parametric survival models visual fits (presented in Appendix A) and statistical fits (presented in Appendix A) to the observed data are discussed alongside the plausibility of the extrapolations.

For the osimertinib arm, the exponential, log-normal and Gompertz distributions were excluded on the basis of poor statistical fit and/or unrealistic long-term extrapolations. The log-logistic gives the closest estimates and the best statistical fit. Generalised gamma and Weibull provide the second and third best statistical fit and similar median OS estimates. For the PDC arm, the log-logistic distribution provides a closer estimate to the flat end of the KM tail, and the most optimistic long-term survival estimates, with some of the best statistical fits in terms of AIC and BIC.

Following the discussion above, the log-logistic was selected as base-case.

Modelling time-to-discontinuation of treatment

A summary of the non-parametric data for TDT from AURA3 is presented below in Table 12.

Table 12 TDT summary data

	Osimertinib (n=279)	**PDC (n=140)**
Total events (%)	252 (90.3%)	136 (97.1%)
Median, months (95% CI)	[redacted]	[redacted]

TDT: Time to Treatment Discontinuation; PDC: platinum-doublet chemotherapy

The TDT KM data for osimertinib from AURA3 DCO4 was applied in the model up to day 1107, after which it was linearly extrapolated. The linear extrapolation offered a good approximation of the visual KM data, with a reasonable extrapolation where all patients have stopped treatment at approximately 42 months. The TDT KM data and extrapolation can be seen in Appendix 9.

For PDC, the TDT KM data from AURA3 DCO3 was effectively complete with less than 1% of patients still on treatment at day 995 (approximately 33 months). Because of this, plus the restriction on the number of chemotherapy cycles, a decision was made not to extrapolate the data beyond the observed period.

A.9 Key model assumptions and inputs

Table 14 and summarises the assumptions and inputs changed in the economic model following the CDF data collection period.

Table 13 Key assumptions and inputs for Model a)

Model input and cross reference	**Original parameter /assumption**	**Updated parameter /assumption**	**Source/Justification**
Overall survival data source for osimertinib App 1	AURAext/2 (November 2015; DC03)	AURAext/2 (May 2018; DC05)	Further follow-up OS data from the pivotal trials AURA2 and AURA Ext (datasets combined) is incorporated into the clinical model
Overall survival extrapolation for osimertinib A.8.1 App 7	Fully fitted independent generalised Gamma parametric curve	Fully fitted Weibull parametric curve	Goodness of fit statistics and visual inspection suggests that the Weibull is the best fitting extrapolation for the updated clinical data

Utilities	Utilities sourced from AURA + IMPRESS PFS: 0.831, SD: 0.751, PD: 0.715, Death: 0	Utilities sourced from AURA + IMPRESS are the most accurate data representative of this patient population. Sensitivity analysis using the ERG preferred utilities from TA416 will be run.

It should be noted that we present the effect of a sensitivity analysis in both Model a) and b), using the ERG's alternative utility values for completeness only. As discussed at the original appraisal, a number of issues with these values should be highlighted:

1. The alternate utility values in the LUME-LUNG 1 study are derived from a different patient population who were not previously treated with an EGFR-TKI and in whom T790M mutation status was unknown.

2. Patients in LUME-LUNG 1 were treated with cytotoxic chemotherapy rather than a tolerable once-a-day tablet formulation such as osimertinib

3. These values do not account for response rates – they simply apply a fixed value of 0.67 for response and stable disease in the PF state. This is despite the Appraisal Committee's recommendation in the original appraisal that the model should account for the benefits of improving overall response rates.

Table 14 Key assumptions and inputs for model b)

Model input and cross reference	Original parameter/assumption	Updated parameter/assumption	Source/Justification
Overall survival			
Data source for osimertinib and PDC. App 2	AURAext/2 (November 2015; DC03)	AURA3 (March 2019; DC04)	New evidence from the RCT AURA3 (became available during the CDF data collection period) is incorporated into the cost effectiveness model
Extrapolation for osimertinib and PDC. App 8 &9	Osimertinib: generalised Gamma parametric curve PDC: Weibull parametric curve	Fully fitted log-logistic parametric curves	Goodness of fit statistics and visual inspection suggests that the log-logistic extrapolation is the best fitting extrapolation for the updated clinical data
Progression-free survival			
Data source for osimertinib and PDC. App 6	AURAext/2 (November 2015; DC03)	AURA3 (March 2019; DC04)	New evidence from AURA3 (become available during the CDF data collection period) is incorporated into the clinical model
Extrapolation for osimertinib and PDC. App 8 & 9	Osimertinib: Gompertz parametric curve PDC: Gompertz parametric curve	Fully fitted Weibull parametric curves	Goodness of fit statistics and visual inspection suggests that the Weibull extrapolation is the best fitting extrapolation for the updated clinical data
Time-to-discontinuation of treatment			
Data source for osimertinib and PDC. App 2	AURAext/2 (November 2015; DC03)	AURA3 (March 2019; DC04)	New evidence from the RCT AURA3 (become available during the CDF data collection period) is incorporated into the clinical model
Extrapolation for osimertinib and PDC. App 8 & 9	KM data + linear extrapolation (osimertinib); KM data (PDC)	KM data + linear extrapolation (osimertinib); KM data (PDC)	Visual inspection suggests that using the KM curve plus a linear extrapolation for the osimertinib arm provides the best fit to the data. And due to the maturity of the data the KM curve for the PDC arm is the most accurate source.
Utilities	Utilities sourced from AURA 3 PFS: 0.836, SD: 0.797, PD: 0.717, Death: 0		Utilities sourced from AURA 3 are the most accurate data representative of this patient population. Sensitivity analysis using the ERG preferred utilities from TA416 will be run.

A.10 Cost-effectiveness results (deterministic)

Table 15 shows the results of the cost-effectiveness analyses submitted for the CDF review. Specifically, six sets of results are presented as requested in the CDF terms of engagement:

(1) Replication of the key cost-effectiveness results considered by committee to demonstrate plausible potential for cost-effectiveness at entry to the CDF (AURAext/2; DCO3);

(2) Cost-effectiveness results that incorporate the latest OS data from AURAext/2 (May 2018; DC05) collected during the CDF data collection period, using company preferred utilities and with all other model inputs and parameters unchanged from cost-effectiveness analysis.

(3) Cost-effectiveness results that incorporate the latest OS data from AURAext/2 (May 2018; DC05) plus any associated changes to the company's preferred assumptions

(3a) Cost-effectiveness results that incorporate the latest OS data from AURAext/2 (May 2018; DC05) plus any associated changes to the company's preferred assumptions and the ERGs preferred utilities

(4) Cost-effectiveness results that incorporate OS, PFS and TDT data from AURA3 (March 2019; DC04) plus any associated changes to the company's preferred assumptions

(4a) Cost-effectiveness results that incorporate OS, PFS and TDT data from AURA3 (March 2019; DC04) plus any associated changes to the company's preferred assumptions and the ERGs preferred utilities

Table 15 Cost-effectiveness results (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry (TA416)							
Osimertinib	£81,631	3.05	1.98	£58,472	1.22	0.83	£70,776
PDC	£23,159	1.82	1.15	-	-	-	-
Model a							
Cost-effectiveness analysis 2: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence (company preferred utilities)							
Osimertinib	£79,846	2.84	2.12	£56,687	1.02	0.82	£69,453
PDC	£23,159	1.83	1.30	-	-	-	-
Cost-effectiveness analysis 3: New company base-case, using company preferred utilities							
Osimertinib	£80,034	2.87	2.14	£56,875	1.05	0.84	£68,015
PDC	£23,159	1.83	1.30	-	-	-	-
Cost-effectiveness analysis 3a: New company base-case, sensitivity analysis, using ERG preferred utilities							
Osimertinib	£80,034	2.87	1.86	£56,875	1.05	0.712	£79,895
PDC	£23,159	1.83	1.15	-	-	-	-
Model b							
Cost-effectiveness analysis 4: AURA 3 analysis, using Company preferred utilities							
Osimertinib	£107,546	3.08	2.30	£73,155	1.03	0.82	£88,877
PDC	£34,278	2.05	1.48	-	-	-	-
Cost-effectiveness analysis 4a: AURA 3 analysis, using ERG preferred utilities							
Osimertinib	£107,546	3.08	1.99	£73,155	1.03	0.70	£104,536
PDC	£34,278	2.05	1.29	-	-	-	-
ICER = incremental cost-effectiveness ratio; LYG = life years gained; PDC = Platinum-doublet chemotherapy; QALYs = quality-adjusted life years							

A.11 Probabilistic sensitivity analysis

Table 16: Updated base-case results (probabilistic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Cost-effectiveness analysis 3: New company base-case, using company preferred utilities							
Model a							
Osimertinib	£80,042	2.89	2.15	£56,868	1.06	0.85	£67,243
PDC	£23,175	1.31	1.31	-	-	-	-
Cost-effectiveness analysis 4: AURA 3 analysis, using company preferred utilities							
Model b							
Osimertinib	£108,182	3.09	2.31	£73,820	1.03	0.83	£89,099
PDC	£34,362	2.05	1.48	-	-	-	-

Figure 10: Scatterplot of probabilistic results (AURAext/2 analysis. Model a)

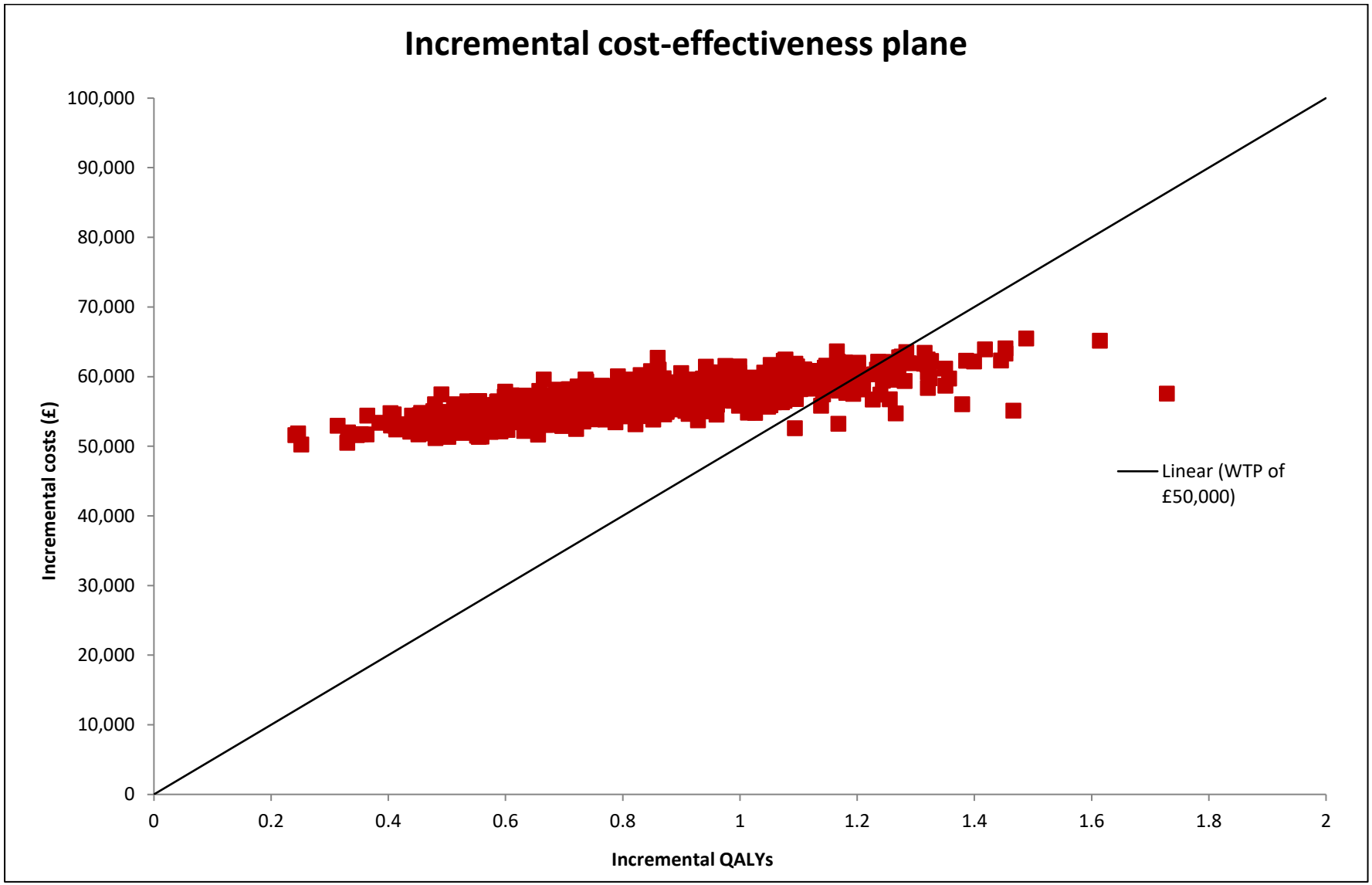
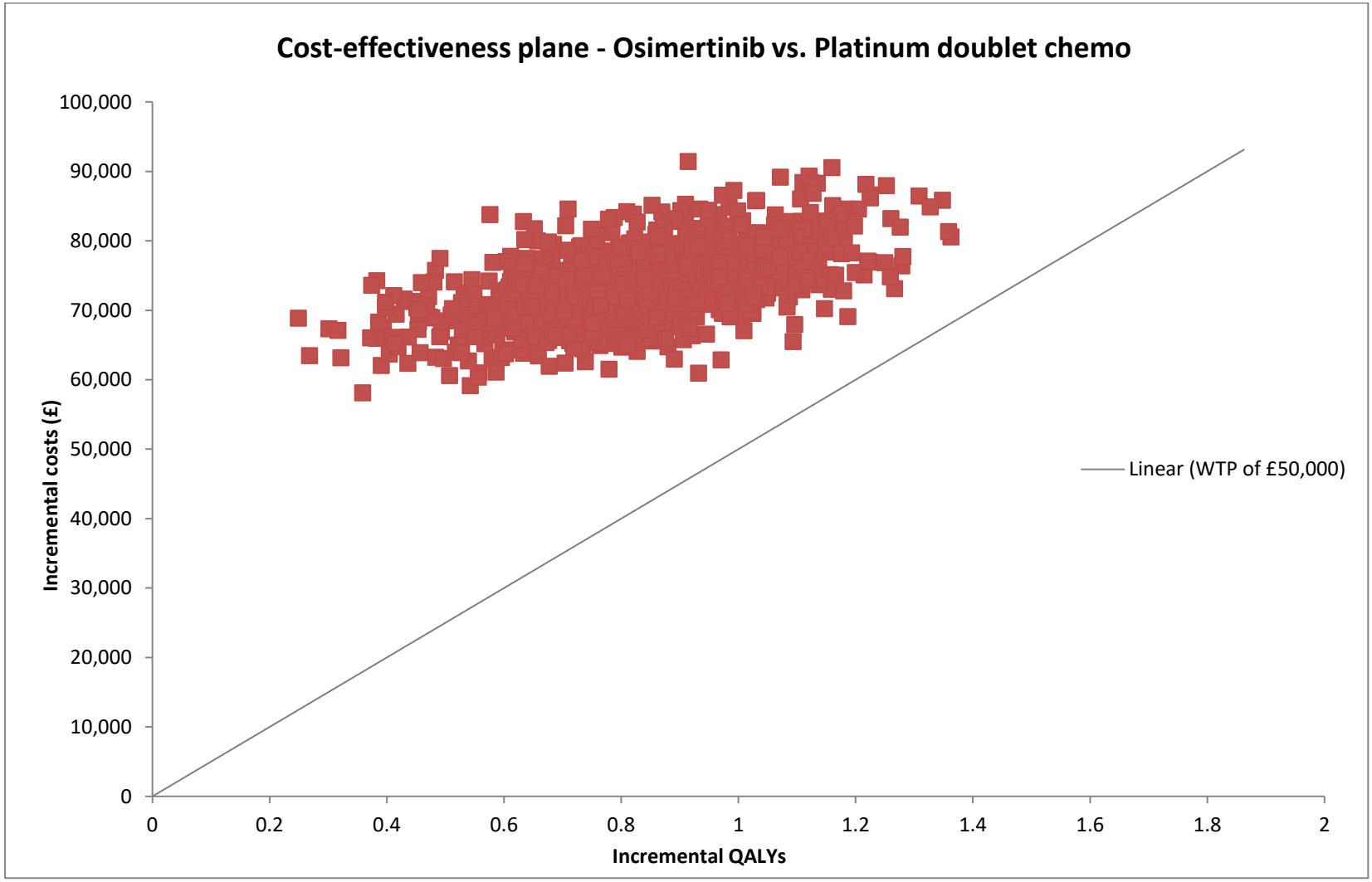


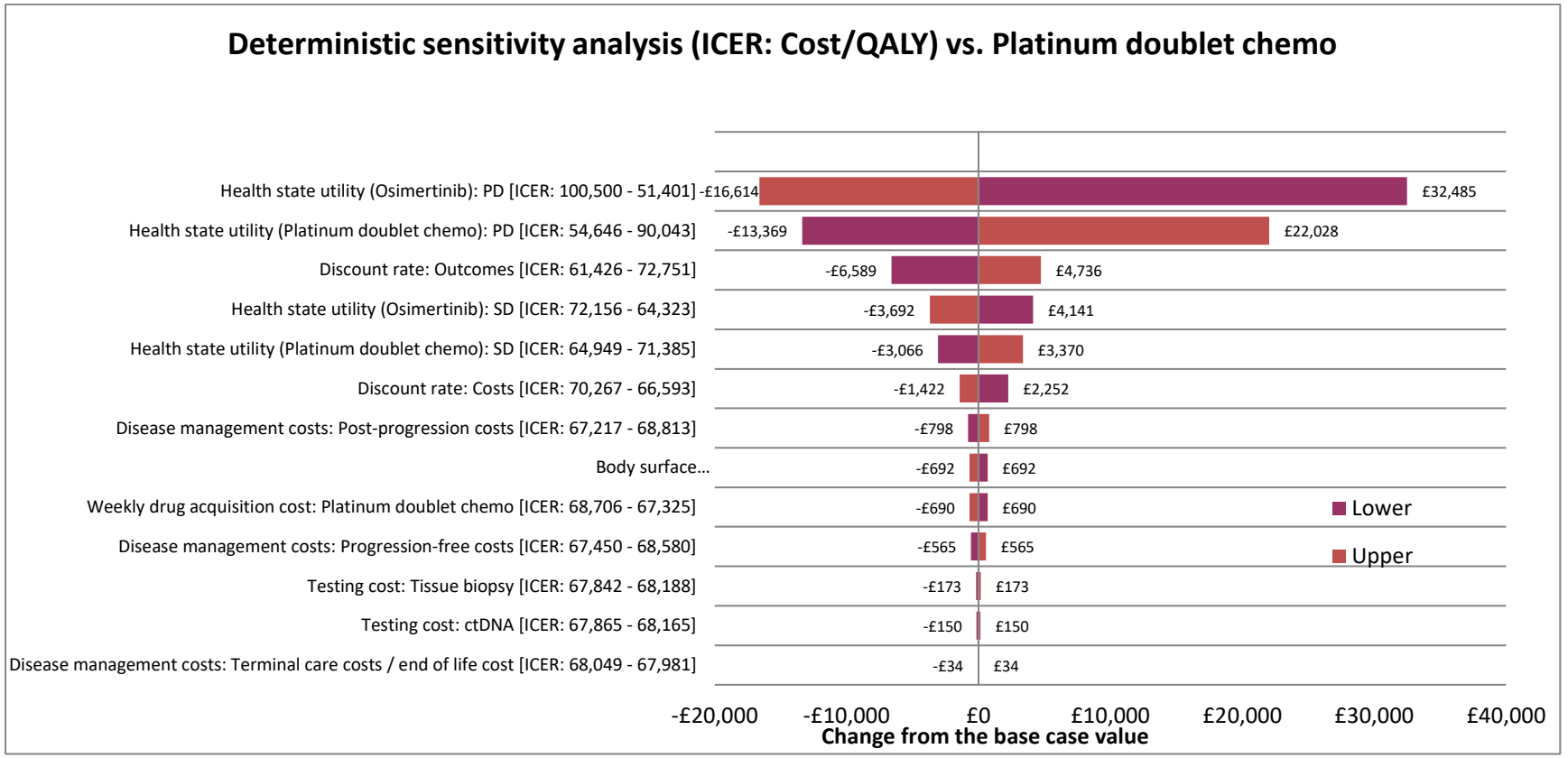
Figure 11: Scatterplot of probabilistic results (AURA 3 analysis. Model b)



A.12 Key sensitivity and scenario analyses

See Table 15 for all scenario analyses.

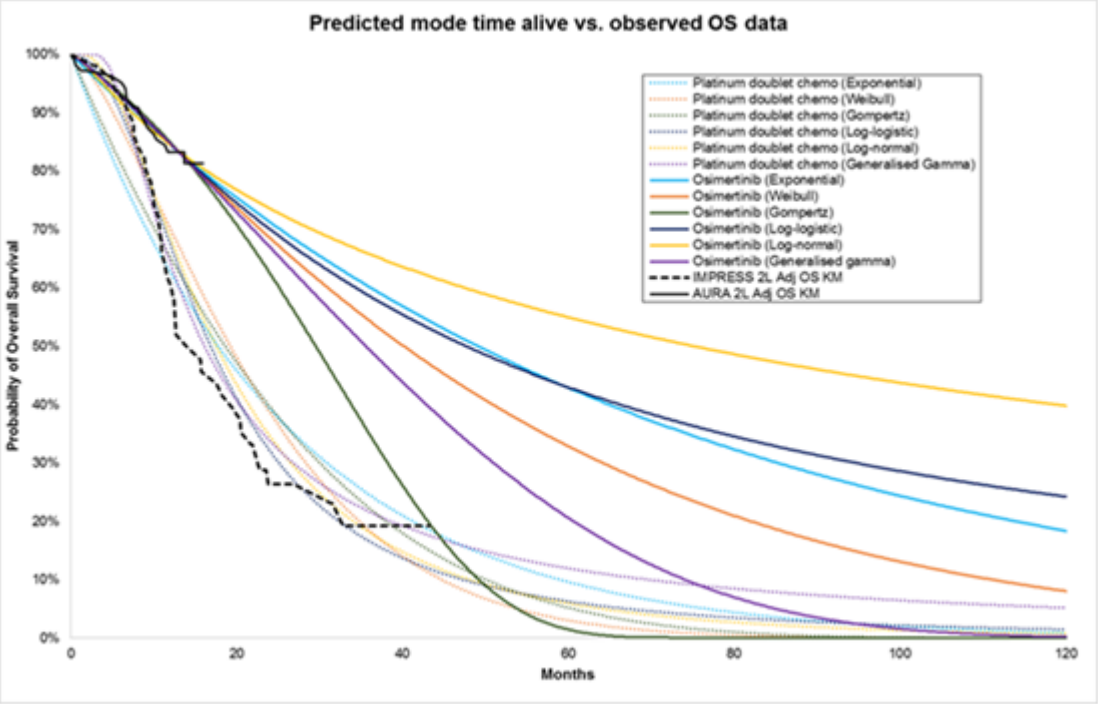
Figure 12: Tornado diagram (base case analysis. Model a)



A.13 Key issues and conclusions based on the data collected during the CDF review period

At the time of the original NICE submission, limited OS follow-up data were available from the AURAext/2 pooled dataset (DCO3 data maturity was 18.5 % (17 events/92 patients for the 2L-only cohort)

Consequently, the fitting of standard parametric survival models led to significant uncertainty in the projected OS outcomes for osimertinib, with median survival estimates ranging from 29.5 months (Gompertz function) to 75.2 months (Log Normal) (see Fig 2. below reproduced from the NICE ACD Response).



Based on visual fit, the Weibull distribution appeared to produce the most reasonable fit to the limited available OS data, resulting in a median OS of 40.2 months. Although the Gompertz and Generalised gamma models produced lower median OS estimates, both extrapolations produced a clinically implausible situation where the OS curves for osimertinib and platinum doublet chemotherapy intersect, resulting in a longer tail of patients still alive in the PDC arm. Conversely it was considered that the Log-normal distribution produced an implausibly high OS estimate for osimertinib and the exponential and log-logistic models provided estimates that also appeared optimistic.

As expected, the availability of mature data from AURAext/2 has resolved some of the uncertainty in the life-expectancy of patients with a T790M mutation receiving osimertinib after progression on a 1st- or 2nd-generation TKI and is in agreement with the survival estimate of similar patients in the AURA3 study.

An expected incremental survival benefit of between 10.6 and 14.6 months in international randomised controlled trials (i.e. AURAext/2 and AURA3) should be considered in the context of the experience of patients within the NHS in England.

	Osimertinib	**PDC**	**Incremental OS benefit**
Original submission (extrapolation)	mOS = 40.2 months	mOS = 19.15 months	20.1 months
Updated AURAext/2 observation	mOS = 28.7 months	mOS = 14.1 months	14.6 months
Updated AURAext/2 model	mOS = [redacted] months (Weibull)	mOS = [redacted] months (Weibull)	[redacted] months
AURA3 observation	mOS = 26.8 months	mOS = 22.5 months (71% cross-over) mOS = [redacted] months (adjusted for cross-over)	4.3 months [redacted] months
AURA3 model	mOS = 27.23 months (log logistic)	mOS = [redacted] months	[redacted] months
Real World Evidence			
CDF SACT data	mOS = 13.9 months		
Non-CDF SACT data		mOS untreated patients = 2.56 months mOS any 2L treatment = 8.31 months	10.4 months 5.6 months

In both controlled studies of osimertinib (AURA3 and AURAext/2), patients who progressed were likely to receive subsequent anticancer therapies (45% of patients in AURA2 who had progressed at DCO3, and 82.4% of osimertinib patients in AURA3 at DCO4).

In contrast, clinical expert opinion in recent appraisals of patients with EGFRm positive advanced/metastatic NSCLC indicate that very few patients in standard NHS practice receive more than a total of 2 or 3 lines of therapy after diagnosis.

> *"The company (Pfizer) indicates that the 2nd line systemic treatment rate in EGFR-mutated NSCLC is 71% and the 3rd line treatment rate is 48%. Both these figures are too high, the likely figures in NHS practice being 50-60% and 25-30%."*
>
> *Cancer Drugs Fund Clinical Lead statement, TA595*

Indeed, analysis of data from SACT, for patients diagnosed in 2014 and 2015, suggests that the actual figures for NHS practice are closer to 33% receiving 2nd line treatments. Unfortunately, the proportion of patients who receive 3 lines of therapy in NHS practice are unavailable at this time. However, it is clear that the attrition rate for patients with EGFRm NSCLC is significantly higher than has typically been observed in clinical trials.

Finally, it is important to note that the median time on treatment for patients receiving osimertinib in the CDF was 9 months (total expected cost within the CDF is approximately [redacted]). The expected improvement in survival for patients is between 5.5 and 10.5 months, given that a proportion of patients who received osimertinib in the CDF, may not have received any subsequent therapy otherwise. It is therefore arguable that the introduction of osimertinib in the CDF has shown to be a cost-effective use of NHS resources.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer (CDF Review of TA416) [ID1577]

Clarification questions

November 2019

File name	Version	Contains confidential information	Date
		Yes/no	
ID1577 osimertinib clarification letter ERG	0.1	Yes	
ID1577 osimertinib clarification letter ERG	0.3	Yes	08/11/2019

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

A1. Please complete/check Table A1 and add source of information.

Table A1: Baseline characteristics across the AURAext/2 pooled and AURA3 trials

Demographic characteristic		AURAext/2 pooled		AURA3	
Indication		≥Second-line (subsequent treatment given when any previous treatments have failed)	Second-line (treatment given when first treatment has failed)	Second-line (treatment given when first treatment has failed)	
Treatment		Osimertinib 80mg	Osimertinib 80mg	Osimertinib 80mg	Platinum Doublet Chemotherapy (PDC)
Number of patients		411	92	279	140
Age (years)	Mean (SD)	62.2 (10.76)	61.77 (11.34)	61.5 (11.64)	62 (11.91)
	Median (min-max)	63 (35-89)	60 (36-89)	62 (25-85)	63 (20-90)
	% ≥65 years	187 (45.5%)	36 (39%)	114 (40.9%)	63 (45%)
Sex	Male	132 (32.1%)	32 (35%)	107 (38%)	43 (31%)
	Female	279 (67.9%)	60 (65%)	172 (62%)	97 (69%)
Smoking	Never	284 (69.1%)	63 (69%)	189 (68%)	94 (67%)
	Ever	114 (27.7%)	29 (31%)	76 (27%)	38 (27%)
	Current	7 (1.7%)		14 (5%)	8 (6%)
EGFR mutation	Exon 19 deletion	279 (67.9%)	67 (73%)	191 (68%)	87 (62%)
	L858R in exon 21	118 (28.7%)	23 (25%)	83 (30%)	45 (32%)
	Other	14 (3.4%)		6 (<3%)	5 (3%)
ECOG / WHO performance system	0	152 (37.0%)	43 (47%)	103 (37%)	56 (40%)
	1	258 (62.8%)	49 (53%)	117 (63%)	84 (60%)
	2	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)
	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	4	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	0–1	410 (99.8%)	92 (100%)	279 (100%)	140 (100%)

Demographic characteristic		AURAext/2 pooled		AURA3	
	2–4	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)
Metastatic at baseline		395 (96.1%)	86 (94%)	266 (95%)	138 (99%)
Brain metastatic at baseline		166 (40.4%)	23 (25%)	93 (33%)	51 (36%)
Race	White	149 (36.2%)	36 (39%)	89 (32%)	45 (32%)
	Asian	247 (60.1%)	55 (60%)	182 (65%)	92 (66%)
	Other	15 (3.7%)	1 (1%)	8 (3%)	3 (2%)

Source: ID874 CS, Table 4.7, Appendix 11: Adjusted Indirect Comparison of Osimertinib vs PDC (ed. 4) and Mok 2017 New England Journal of Medicine publication

A2. Please complete Table A2 and add source of information.

Table A2: Results from the AURAext/2 pooled and AURA3 trials

Outcome		AURAext/2 pooled		AURA3	
Indication		≥Second-line (treatment given when any previous treatments have failed)	Second-line (treatment given when first treatment has failed)	Second-line (treatment given when first treatment has failed)	Second-line (treatment given when first treatment has failed)
Treatment		Osimertinib 80mg	Osimertinib 80mg	Osimertinib 80mg	Platinum Doublet Chemotherapy (PDC)
Sample size		411	92	279	140
ORR	Patients with responses (%)	262/397 (66.1%)	60 (67.4%)	181 (64.9%)	48 (34.3%)
PFS	Total events (%)	280 (68.1%)	64 (69.6%)	140 (50.2%)	110 (78.6%)
	Median (95% CI)	9.9 (9.5, 12.3)	9.7 (	10.1 (8.3, 12.3)	4.4 (4.2, 5.3)
OS	Total events (%)	271 (65.9%)	56 (60.9%)	188 (67.4%)	93 (66.4%)
	Median (95% CI)	26.3 (24.0, 29.1)	28.7 (24.8, 36.2)	26.81 (23.49, 31.54)	22.47 (20.17, 28.81)

Source: Appendix 11: Adjusted Indirect Comparison of Osimertinib vs PDC (ed. 4), Appendix 2; AURA3 CSR (Aug 2019) and Appendix 10; AURA3 CSR (Nov 2016).

Section B: Clarification on cost-effectiveness data

B2. Priority request. Please provide time-to-death from any cause (overall survival) Kaplan-Meier analysis of the March 2019 AURA-3 data for both treatment arms. In particular, please provide the following analyses:

(i) Overall survival (base case, Rank Preserving Structural Failure Time adjusted [on treatment, acceleration factor only])
(ii) Progression-free survival
(iii) Time to treatment discontinuation

Please present analysis outputs using the format used in the sample table below

Example table: Example of output (SAS) required from specified Kaplan-Meier analyses

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		**……**	**……**	**……**	**…**	**…**
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1

999.000		0	1.0000	0	57	0

Section C: Textual clarification and additional points

C1. In the company submission for this review (Section A.13, p39) there is a table displaying incremental median OS data. In the last row of that table the data seem to suggest that the median OS difference between CDF SACT data and non-CDF SACT data for untreated patients is 10.4 months. If this is the correct number, please clarify how it was calculated as the ERG calculate the difference to be 11.34 months (13.9-2.56=11.34).

Apologies. The ERG calculation is correct. The calculation used in the submission should be corrected.

C2. Priority request. Please could you provide copies of the following three documents:

- AURA3 Clinical Study Report Edition 2, dated 9 November 2016
- Full technical report for the Matched Adjusted Indirect Comparison (as mentioned in appendix 7)
- The Statistical Analysis Plan for AURA3

The documents are provided as Appendices 10, 11 and 12.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer [ID1577]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	EGFR Positive UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	EGFR Positive UK is a patient-led, patient-driven support group with over a hundred members across the UK. It is currently self-funded by patients with the intent to register as a charity in early 2020. The organisation has an active Facebook group which is closed space for EGFR lung cancer patients and their families. The organisation also has a website - www. egfrpositive.org.uk - which offers information and support to patients and their families. We have been recognised by leading charities, medical groups and the pharmaceutical industry as advocates for EGFR lung cancer patients in the UK.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Members were invited on our Facebook group to submit comments and their experiences of being on osimertinib for EGFR T790M mutation positive lung cancer via email.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	EGFR Positive UK is an organisation which supports over one hundred EGFR positive lung cancer patients and their families. Many of our members are younger, often never-smokers, and almost all of them were diagnosed with stage IV lung cancer. Approximately 90% of our members receive their treatment via the NHS and are generally prescribed afatanib or gefitinib as their first line TKI. About 50% of our members whose first treatment fails, go on to develop the T790M mutation and then move onto osimertinib as a second line treatment. Availability of this drug is crucial for the population who go on to develop T790M. There are few treatment options for EGFR mutated lung cancer patients and access to osimertinib in this scenario is crucial, both in terms of the benefit for overall survival, and the proven CNS control and lack of side effects associated with this drug. Crucially, our members testify that quality of life is significantly improved on osimertinib, both in terms of side effects and time spent at hospital appointments or receiving treatment for side effects. AH writes, ‘On afatanib, I lost a lot of confidence, worrying if eating out I would get diarrhoea even after taking loperamide before the meal. With osimertinib, I don’t have this worry and I have got my confidence back which has enabled me to go abroad twice this year which I would never have contemplated before’. After progressing on afatanib, another patient, SG comments ‘I had three litres of fluid drained from my right lung as I was having difficulty breathing and had also developed brain mets. On osimertinib I feel very well again, I can breathe normally, and my oncologist expects it to treat my brain mets. It is very easy to take and has minimal side effects compared to other treatments. My quality of life has dramatically improved’. KB has been on osimertinib for three and a half years: ‘Prior to this I had chemo, Tarceva and Rocilitinib for varying amounts of time. All the previous meds had horrid and debilitating side effects. The other TKIs prevented me from having a normal life with my husband. I could not go out to a restaurant or on holiday

	and my life revolved around being close to a W.C. I had several incidents where I didn't make it to a toilet in time, and I cannot tell you how embarrassing that was or the damage it did to my self-confidence. Since starting osimertinib, I have as near to my normal life as possible. I holiday, I socialize, I support others with lung cancer, eat whatever I want, and I have regained my confidence. Everyone should have the opportunity to take this drug and have the best possible life with lung cancer'. A significant number of our members are younger and have dependent children - in the last week a thirty-seven year- old father with three children of six, three and five months and a forty-three year- old mother with a ten and an eight year- old have been amongst those who have joined our group. The ability to continue to support the family financially, and to fully partake in family life is vital for these parents. Again, access to osimertinib and its side effect profile facilitates this. The prognosis for lung cancer patients is poor, but in the time which patients do have left to be with their families, which can be significantly extended by osimertinib, the quality of life benefits cannot be underestimated. If osimertinib were not available, the only option for these patients would be chemotherapy which does not offer the same OS benefit and comes with a significant reduction in quality of life for all patients. For members who are still taking first or second generation TKIs, the availability of osimertinib provides significant hope that if they go on to develop T790M there will be another targeted option for them. Similarly, for patients with brain metastases in combination with T790M, osimertinib offers effective CNS control without the side effects of WBRT or SBRT - the alternative treatment options. As PW writes, 'I am currently on afatanib but my oncologist wants me to take this drug when I have progression. He knows it will work for me and I am grateful that I might have this option'.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers benefit massively from targeted therapy drugs but there still very limited treatment options when resistance to these targeted therapies develops. Apart from chemotherapy, osimertinib for EGFR T790M positive NSCLC is the only targeted option currently available for patients on the NHS. There need to be more effective options for EGFR resistant NSCLC.
8. Is there an unmet need for patients with this condition?	See above
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	OS benefit, minimal side effect profile, proven CNS benefit. It is easy to administer and cuts down on the amount of time patients spend in hospital dealing with or requiring input from their medical teams with side effects. Many patients are able to go for two or three months without seeing their medical team when they are stable on this treatment.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	None

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It is crucial that all patients who may be eligible to take this drug in this scenario have the genetic profiling either through tissue or liquid biopsy to identify whether they have a T790M mutation. T790M is often hard to find and we have cases in which members have had to push very hard for a second blood biopsy or a tissue biopsy in order to hunt for the mutation. In many cases it has found on second or even third attempt. We are concerned that some patients will not have the knowledge or confidence to insist on a follow-up biopsy in this scenario.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages
15. In up to 5 bullet points, please summarise the key messages of your submission: ● The technology offers significant OS benefit ● The technology offers significant QOL benefit ● It offers proven CNS benefit ● It is easy to administer and cuts down on hospital attendance and treatments for side effects associated with other treatments ● There are limited other options for EGFR positive NSCLC patients who develop resistance to first and second generation TKIs.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer [ID1577]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	On behalf of NCRI-ACP-RCP-RCR

3. Job title or position	RCP registrar
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	NCRI-ACP-RCP-RCR
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	The main aim of osimertinib as second-line treatment in patients with T790M mutation positive advanced non-small cell lung cancer (NSCLC) is to palliate – to improve symptoms, maintain quality of life, control disease, and increase survival.

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The main alternative second-line treatment option for this patient population is platinum-based chemotherapy. The randomised, open-label, phase III, AURA3 trial (Mok et al. N Eng J Med 2017. 376(7):629-40), compared osimertinib to platinum-based chemotherapy in this patient population. This study reported a median progression free survival (PFS) in the control arm (platinum-pemetrexed chemotherapy) of 4.4 months by investigator assessment, which is consistent with other chemotherapy studies in this patient population. A 50% improvement in PFS would be clinical significant. The AURA3 study reported an improvement in median PFS to 10.1 months with osimertinib treatment, which is both statistically and clinically significant. Of note, PFS estimates as measured by independent central radiology review were similar.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Gefitinib, erlotinib, afatinib or dacomitinib are oral tyrosine kinase inhibitor (TKI) agents currently offered as first-line therapy for advanced epidermal growth factor receptor (EGFR) mutation positive NSCLC. Patients that progress on first-line EGFR TKI are re-tested for the presence of the T790M resistance mutation. Patients

	with tumours that develop this resistance mutation are currently offered osimertinib treatment through the Cancer Drug Fund (CDF). EGFR mutation positive NSCLC patients whose tumours do not develop this resistance mutation are offered alternative treatment options at progression, currently either a combination of platinum-based chemotherapy plus immunotherapy plus vascular targeted therapy (as per CDF – TA584), platinum-based chemotherapy, continuation with first-line EGFR TKI despite disease progression, or best supportive care. These options would apply to NSCLC patients that develop the T790M resistance mutation if osimertinib were to be withdrawn.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidance: Lung cancer: diagnosis and management (NG122)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS?	Yes – well defined: CDF access to osimertinib has allowed oncology centres to establish pathways for EGFR mutation positive advanced NSCLC patients that have progressed on first line therapy to undergo testing (circulating tumour (ct) DNA or tumour biopsy) to evaluate for the presence of the T790M mutation. If presence of the mutation is confirmed, patients are then switched to osimertinib following application to the CDF.
• What impact would the technology have on the current pathway of care?	For patients with the T790M mutation, osimertinib has proved to be a very well tolerated treatment in our day to day practice, with a greatly superior toxicity profile compared to the main treatment alternative - platinum-based chemotherapy. Taking this into account, alongside the AURA3 trial data showing improved survival outcomes, removing access to this technology would be a backward step in the current pathway of care.
10. Will the technology be used (or is it already used) in	Yes

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	NA
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist oncology clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Access to testing for the T790M mutation, which is now well established.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase	As per results of the AURA3 study, osimertinib improves responses rate and PFS with reduced severe toxicity rates compared to platinum-based chemotherapy. Overall survival (OS) was a secondary endpoint for

length of life more than current care?	AURA3, and the OS data is not yet mature, although results will be confounded by a high crossover rate. Long-term non-randomised outcome data suggest promising survival outcomes in this patient population (Ahn M et al. Cancer 2019. 125(6):892-901).
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – as reported by the AURA3 study, compared to chemotherapy, treatment with osimertinib was associated with lower rates of severe treatment-related toxicities. In addition, patient reported outcome measures demonstrated superior symptom control and improved patient function with osimertinib (Lee CK et al. J Clin Oncol 2018. 36(18):1853-60).
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Osimertinib is recommended and considered in this guidance specifically for patients with advanced EGFR mutation positive NSCLC that has progressed after first line EGFR TKI in the presence of the T790M resistance mutation.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	NA

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment will continue until lack of clinical benefit/unacceptable toxicity.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	CNS metastases are a significant issue in this patient population. In the AURA3 study population, 116/419 (27.7%) had measurable and/or non-measurable CNS lesions. Osimertinib treatment was associated with improved CNS penetration and activity against CNS metastases compared to platinum-based chemotherapy (Wu YL et al. J Clin Oncol 2018. 36(26):2702-09).
16. Do you consider the technology to be innovative in its potential to make a	Yes

significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes – there is a clear need to provide alternative targeted therapies for advanced EGFR mutation positive lung cancer.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The clinical experience in daily practice, and as reported by the AURA3 study, is of a much improved toxicity profile for osimertinib compared to the alternative of platinum-based chemotherapy treatment.
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	NA
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes – response rate, PFS, safety profile and patient reported outcome measures. OS data is still awaited.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	Published summary real-world data indicate results consistent with the trial data (Marinis F et al. Future Oncol 2019. 15(26):3003-14).
Equality	
22a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.]	

if there are none delete highlighted rows and renumber below	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- The AURA3 data indicates superior outcomes with respect to response rate, PFS, toxicity profile and patient reported outcome measures compared to platinum-based chemotherapy.
- The AURA3 OS data is still immature.
- Withdrawing patient access to osimertinib would be a backwards step in the current patient pathway.
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Public Health England

Protecting and improving the nation's health

Osimertinib for treating previously treated metastatic epidermal growth factor receptor and T790M mutation-positive non-small-cell lung cancer review

Commissioned by NHS England

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. We do this through world-leading science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. We are an executive agency of the Department of Health and Social Care, and a distinct delivery organisation with operational autonomy. We provide government, local government, the NHS, Parliament, industry and the public with evidence-based professional, scientific and delivery expertise and support.

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Contents

Executive summary

Introduction

In July 2016, The National Institute for Health and Care Excellence (NICE) Appraisal Committee evaluated the clinical and cost effectiveness of osimertinib in patients diagnosed with metastatic EGFR and T790M mutation-positive non-small cell lung cancer (NSCLC). The committee highlighted clinical uncertainty around estimates of treatment duration and overall survival (OS) in the evidence submission. As a result, they recommended commissioning of osimertinib through the Cancer Drugs Fund (CDF) to allow a period of managed access, including additional data collection, to solve clinical uncertainty.

NHS England commissioned Public Health England (PHE) to evaluate the 'real-world' treatment effectiveness of osimertinib in the CDF population. This report presents the results of that real-world use of osimertinib, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report and the data presented demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to get access to promising new treatments much earlier than might otherwise be the case, while further evidence is collected to address clinical uncertainty.

The NHS England and Public Health England partnership for collecting and following up real-world SACT data in the CDF in England has resulted in analysis of data for the full patient population and almost 100% data completion. PHE and NHS England are committed to providing world-first, high quality and real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England's Blueteq system was used to provide a reference list of all patients with an application for osimertinib for NSCLC in the CDF. Patient NHS numbers were used to link Blueteq applications to PHE's routinely collected SACT data to provide SACT treatment history.

Between October 2016 and September 2018, 386 applications for osimertinib were identified in the NHSE's Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 357 patients were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

All 357 (100%) unique patients with CDF applications were reported in the SACT dataset.

Median treatment duration for the analysis cohort was 9 months (274 days) [95% CI: 8.3,10.1]. 64% [95% CI: 58%, 68%] of patients were receiving treatment at 6 months and 37% [95% CI: 31%, 43%] of patients were receiving treatment at 12 months.

The median OS was 13.9 months (423 days) [95% CI: 12.1, 17.6]. By the end of the data collection period, 180 patients (50%) had died. OS at 6 months was 78% [95% CI: 74%, 82%], OS at 12 months was 56% [95% CI: 50%, 62%].

At data cut off, 208 patients were identified as no longer being on treatment; 63% (N=130) patients had stopped treatment due to disease progression, 3% (N=6) of patients had stopped treatment due to toxicity, 5% (N=10) of patients chose to end their treatment, 18% (N=38) of patients died (not on treatment) and 12% (N=24) of patients died on treatment.

Sensitivity analysis was conducted for a cohort with at least 6 months data follow-up in the SACT dataset. Results were consistent with the full analysis cohort.

Introduction

Lung cancer is the third most common cancer diagnosed in England and accounts for around 38,381 cancer diagnoses in 2016[2]. There are 2 main groups of lung cancer: small cell lung cancer and NSCLC. NSCLC is the most common type of lung cancer, constituting around 12,000 cases diagnosed in males and 10,000 diagnosed in females[3].

Most lung cancers are diagnosed at an advanced stage, when the cancer has spread to lymph nodes and other organs (stage III) or metastasised, spreading to distant parts of the body (stage IV). In 2017, results published by National Cancer Registration and Analysis Service[4] (NCRAS) showed that 19% of patients diagnosed with lung cancer were diagnosed with stage III and 47% of patients were diagnosed with stage IV[5].

People with NSCLC can over-express the epidermal growth factor receptor (EGFR) and in these cases patients EGFR tyrosine kinase inhibitor (EGFR-TKI) treatments are effective. In some patients with EGFR-positive disease a mutation can occur at position 790 of the EGFR protein (T790M). This mutation may be present before treatment or arise during EGFR-TKI treatment and generally results in resistance to EGFR-TKIs. The T790M mutation accounts for approximately 50% of EGFR-TKI resistance[6].

Osimertinib is a small molecule, oral EGFR-TKI and is a treatment option for patients diagnosed NSCLC who are EGFR T790M positive.

Background to this report

The Public Health England and NHS England partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England and PHE's ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the PHE and NHS England partnership on cancer data is to address mutually beneficial questions using SACT data collected by PHE. This includes NHS England commissioning PHE to produce routine outcome reports on patients receiving treatments funded through the CDF during a period of managed access.

The CDF is a source of funding for cancer drugs in England[7]. From the 29 July 2016, NHS England, in partnership with NICE, implemented a new approach to the appraisal and funding of cancer drugs. The CDF operates as a managed access scheme, providing patients with earlier access to new and promising treatments where there is significant uncertainty as to their clinical and cost effectiveness. During the period of managed access, data is collected to address the uncertainties identified by the NICE appraisal committee. A report on this data is produced at the end of the CDF managed access period for the review of each topic[8].

PHE analyse data derived from patient-level information collected within the NHS, as part of the routine care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the NCRAS, which is part of PHE.

NICE Appraisal Committee appraisal of osimertinib in treating metastatic EGFR and T790M mutation-positive NSCLC [TA416]

The NICE Appraisal Committee appraised the clinical and cost effectiveness of osimertinib in treating metastatic EGFR and T790M mutation-positive NSCLC [TA416] and NICE published the guidance for this indication in October 2016[9].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended commissioning of osimertinib through the CDF for a period of 30 months, from October 2016 to March 2019.

Results from ongoing clinical trials evaluating osimertinib in the licensed indication are expected to answer many of the clinical uncertainties raised by the NICE committee. The ongoing trials that will support the reappraisal of osimertinib by NICE are the AURA extension clinical trials (AURA2 and AURA3).

This report provides real-world information on the use of osimertinib in England – outside of the clinical trial setting – and acts as a secondary source of information

alongside the results of the AURA2 and AURA3 clinical trials[10]. The key areas of uncertainty identified by the committee for re-appraisal at the end of the CDF data collection are:

- treatment duration for the use of osimertinib
- OS from the start of a patient's first treatment with osimertinib

Approach

Upon entry to the CDF, representatives from NHS England, NICE, PHE and the company (AstraZeneca) formed a working group to agree the Data Collection Agreement (DCA). The DCA set out the real-world data to be collected and analysed to support NICE's reappraisal of osimertinib. It also detailed the eligibility criteria for patient access to osimertinib through the CDF and CDF entry and exit dates.

This report includes patients with approved CDF applications (via Blueteq) for osimertinib, followed-up in the SACT dataset collected by PHE.

Methods

CDF applications - identification of the cohorts of interest

NHS England collects applications for CDF treatments through its online prior approval system, Blueteq. The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes.

Consultants must complete a Blueteq application form for every patient receiving CDF-funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. NHS England shares an extract from the Blueteq database with PHE on a monthly basis. This extract contains NHS numbers, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria). The data exchange is governed by a data sharing agreement between NHS England and PHE.

PHE collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Osimertinib clinical treatment criteria

The criteria are:

- application made by – and first cycle of SACT to be prescribed by – a consultant specialist specifically trained and accredited in the use of SACT
- histologically- or cytologically-documented NSCLC that carries an EGFR and a T790M mutation
- locally-advanced or metastatic NSCLC
- radiological documentation of disease progression following first line EGFR TKI treatment with only 1 TKI and without any further systemic anti-cancer treatment
- treatment with no more than 1 prior line of treatment for advanced NSCLC
- no prior chemotherapy unless any prior neoadjuvant or adjuvant chemotherapy had been completed at least 6 months prior to starting first line EGFR treatment
- performance status of 0 or 1
- at time of starting osimertinib the patient must be fit enough to have potentially started platinum-based doublet chemotherapy

CDF applications – de-duplication criteria

Before conducting any analysis on CDF treatments, the CDF database is examined to identify duplicate applications. The following de-duplication rules are applied:

If 2 trusts apply for osimertinib for the treatment of locally advanced or metastatic EGFR and T790M mutation-positive NSCLC for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

If 2 trusts apply for osimertinib for the treatment of locally advanced or metastatic EGFR and T790M mutation-positive NSCLC for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected – even if the CDF trust did not match the SACT treating trust.

If 2 applications are submitted for osimertinib for the treatment of locally advanced or metastatic EGFR and T790M mutation-positive NSCLC and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

Initial CDF cohorts

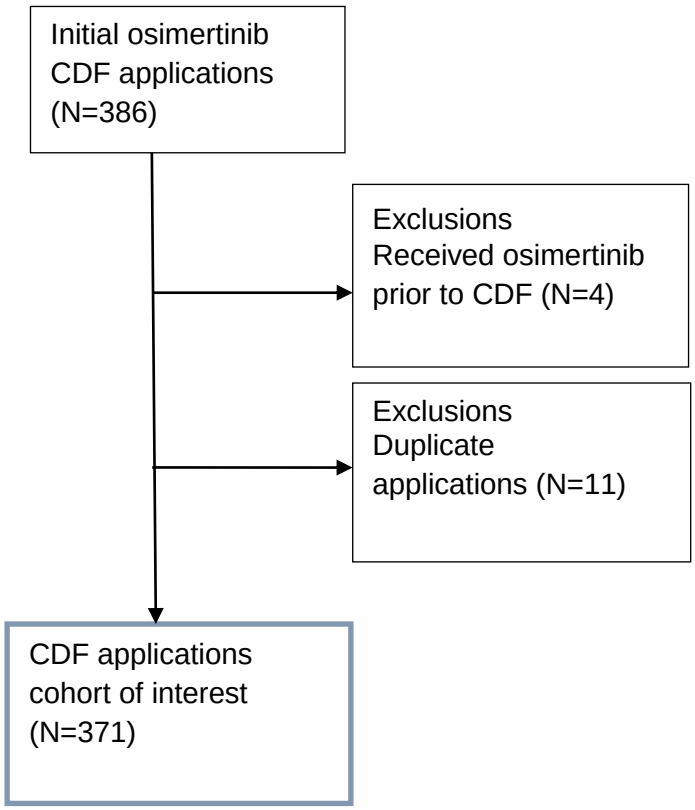
Analysis is limited to the date osimertinib entered the CDF for this indication onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme or a compassionate access scheme run by the pharmaceutical company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the managed access agreement for this indication.

The CDF applications included in these analyses have been limited to between 4 October 2016 and 4 September 2018. A snapshot of SACT data was taken on 5 January 2019 and made available for analysis on 11 January 2019. The snapshot includes SACT activity up to 30 September 2018. Tracing the patients' vital status was carried out on 15 January 2019 using the PDS[1].

There were 386 applications for CDF funding for osimertinib for treating locally-advanced or metastatic EGFR and T790M mutation-positive NSCLC between 4 October 2016 and 4 September 2018 in the NHSE Blueteq database. Following deduplication this relates to 375 unique patients.

An additional 4 patients were excluded from these analyses as they appeared to have received osimertinib prior to the drug being available through the CDF.

Figure 1: Derivation of the cohort of interest from the initial CDF applications made for osimertinib for locally advanced or metastatic EGFR and T790M mutation-positive NSCLC between 4 October 2016 and 4 September 2018.



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for osimertinib in NHS England's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application. This includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT. Treatment start date is defined as the date the patient started their CDF treatment. This date is identified in the SACT dataset as the patient's earliest treatment date for the treatment of interest. Data items used to determine a patient's earliest treatment date are:

- start date of regimen – SACT data item #22
- start date of cycle – SACT data item #27
- administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34) are used to identify a patient's final treatment date. The latest of these 3 dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

Start date of regimen
A regimen defines the drugs used, their dosage and the frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle
A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment; after each treatment administration there will be a delay before the next treatment administration. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The patient's next cycle would start on the 21st day.

Administration date
An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above as an example, the administrations for a 3-weekly cycle would be on the 1st and 8th day and then again on the 21st day, which would be the first day of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment. All patients are then allocated a prescription length, which is a set number of days added to the final treatment date to allow for the fact that they are effectively still on treatment until the next administration. The prescription length should correspond to the typical duration for which the drug is prescribed.

If a patient dies between administrations, then their censor date is their date of death. These patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database that the patient ended treatment due to disease progression or toxicity before death.

Parenteral drugs are generally administered in a healthcare facility and healthcare professionals are able to confirm that treatment administration has taken place on a specified date. In contrast, a course of oral tablets will be prescribed and taken by the patient outside of a healthcare facility. While it is not always possible to validate that a patient has taken an oral treatment (based on clinical feedback and product guidance), a 28-day duration has been added to final treatment date for all patients. This represents the number of tablets typically prescribed at the start of each cycle.

Treatment duration is calculated for each patient as:
Treatment duration (days) = (final treatment date – treatment start date) + prescription length (days).

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as 1 of the following:

No longer receiving treatment (event), if:

- the patient has died
- the outcome summary (SACT data item #41) detailing the reason for stopping treatment has been completed
- there is no further SACT records for the patient following the period of the treatment end indicator

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead/alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = date of death (or follow up) – treatment start date

The patient is flagged as either:

Dead (event):
At the date of death recorded on the PDS.

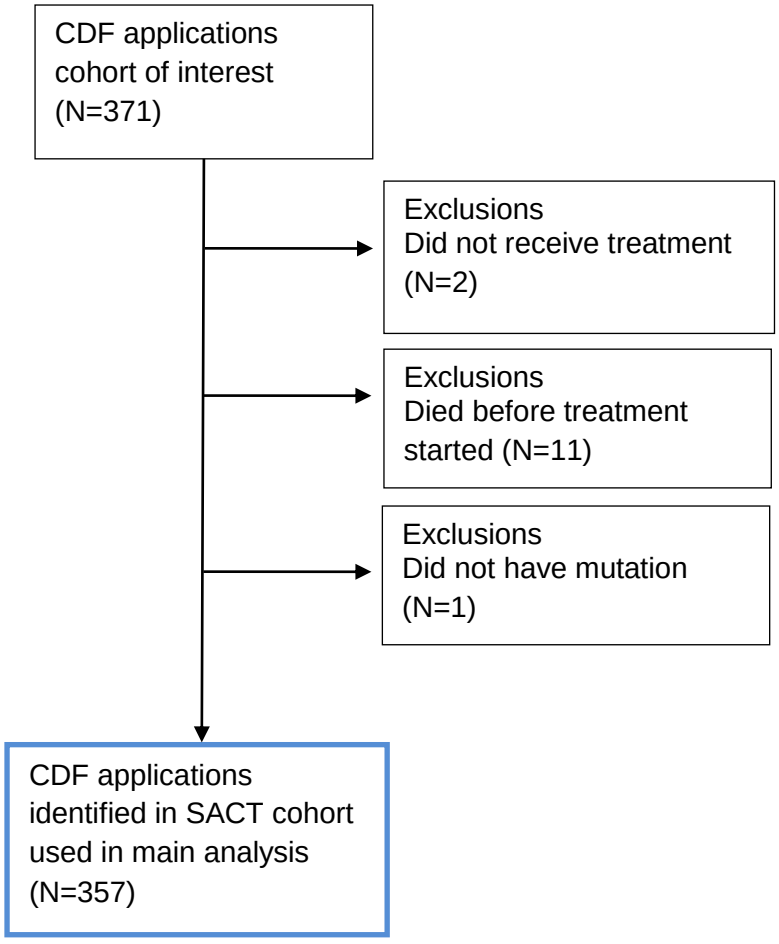
Alive (censored):
At the date patients were traced for their vital status as we know patients were still alive on this date.

Results

Cohort of interest

Of the 371 new applications for CDF funding for osimertinib for locally advanced or metastatic EGFR and T790M mutation-positive NSCLC, 1 patient did not have the T790M mutation, 2 patients did not receive treatment and 11 patients died before treatment started (see Figure 2).

Figure 2: Matched cohort – SACT data to CDF (Blueteq) applications for osimertinib for locally-advanced or metastatic EGFR and T790M mutation-positive NSCLC between 4 October 2016 and 4 September 2018.



A maximum of 357 osimertinib records are expected in SACT for patients who were still alive and eligible to commence treatment (Figure 2). 100% (357/357) of these applicants for CDF funding had a treatment record in SACT.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is >90% for all key items and 100% for primary diagnosis, date of birth, gender and treatment dates.

Table 1: Completeness of key SACT data items for the osimertinib cohort (N=357)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Sex	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	91%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died or has not received treatment with osimertinib in at least 3 months. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 208 patients. Of these, 208 have an outcome summary recorded in the SACT dataset 100% (208/208).

Table 2: Completeness of outcome summary for patients that have ended treatment (N=208)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	100 %

Patient characteristics

The median age of the 357 patients receiving osimertinib was 67 years. The median age in males and females was 69 and 66 years respectively.

Table 3: Patient characteristics (N=357)

Patient characteristics[1]			
		Frequency (N)	**Percentage (%)**
Sex	Male	116	32%
	Female	241	68%
Age	<40	2	1%
	40-49	21	6%
	50-59	79	22%
	60-69	111	31%
	70-79	101	28%
	80+	43	12%
Performance status	0	81	24%
	1	219	61%
	2	21	6%
	3	5	1%
	4	0	0%
	Unknown	31	9%

[1] Figures may not sum to 100% due to rounding.

Treatment duration

Of the 357 patients with CDF applications, 208 (58%) were identified as having completed treatment by 30 September 2018. Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with osimertinib in at least 3 months (see Table 4). The median follow-up time in SACT was 196 days.

Presently, 60% of trusts submit their SACT return to the submission portal 2 months after the month's treatment activity has ended, this provides a maximum follow-up period of 24 months. 40% of trusts submit their SACT return to the submission portal 1 month after the month's treatment activity has ended, this would provide the maximum follow-up period of 25 months. The end date of follow-up is 30 September 2018.

Table 4: Breakdown by patients' treatment status[2,3]

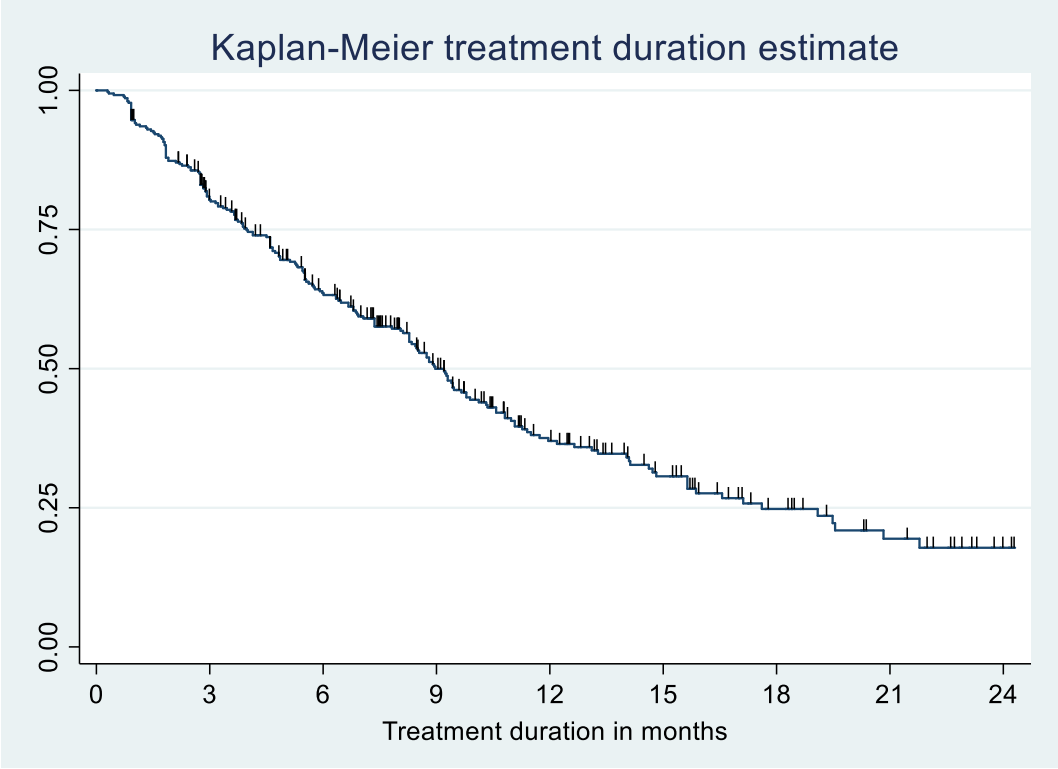
Patient status	Frequency (N)	Percentage (%)
Patient died - on treatment	24	7%
Patient died - not on treatment	156	44%
Treatment stopped	28	8%
Treatment ongoing	149	42%
Total	357	

The Kaplan-Meier curve for ongoing treatment is shown in figure 3. The median treatment duration for all patients was 9 months [95% CI: 8.3, 10.1] (N=357). Patients receiving treatment at 6 months was 64% [95% CI: 58%,68%], patients receiving treatment at 12 months was 37% [95% CI: 31%, 43%].

[2] Figures may not sum to 100% due to rounding.

[3] Table 7 presents the outcome summary data reported by trusts. This includes patients from Table 4 that 'died on treatment', 'died not on treatment' and 'stopped treatment'.

Figure 3: Kaplan-Meier treatment duration (N=357)



Tables 5 and 6 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for treatment duration was 24 months.

Table 5: Number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0 - 24	3 - 24	6 - 24	9 - 24	12 - 24	15-24	18-24	21-24	24
Number at risk	357	268	186	120	69	44	24	13	2

Table 6 shows that for all patients who received treatment, 149 were still on treatment (censored) at the date of follow-up and 208 had ended treatment (events).

Table 6: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored).

Time intervals (months)	0 - 24	3 - 24	6 - 24	9 - 24	12 - 24	15-24	18-24	21-24	24
Censored	149	129	100	70	47	32	19	12	2
Events	208	139	86	50	22	12	5	1	0

Table 7 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 58% (N=208) of patients had ended treatment at 30 September 2018.

Table 7: Treatment outcomes for patients that have ended treatment (N=208)[4,5]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	130	63%
Stopped treatment – acute chemotherapy toxicity	6	3%
Stopped treatment – patient choice	10	5%
Stopped treatment – died not on treatment	38	18%
Stopped treatment – died on treatment	24	12%
Total	208	

[4] Figures may not sum to 100% due to rounding.

[5] Table 7 presents the outcome summary data reported by trusts. This includes patients from Table 4 that 'died on treatment', 'died not on treatment' and 'stopped treatment'.

Overall survival

Of the 357 patients with a treatment record in SACT, the minimum follow up was 4 months from the last CDF application. Patients were traced for their vital status on 15 January 2019, this date was used as the follow-up date (censored date) if a patient is still alive.

Figure 4 provides the Kaplan-Meier curve for OS, censored at 15 January 2019. The median survival was 13.9 months [95% CI: 12.1, 17.6] (N=357). Survival at 6 months was 78% [95% CI: 74%, 82%], 12 months survival was 56% [95% CI: 50%, 62%].

Figure 4: Kaplan-Meier survival plot (N=357)

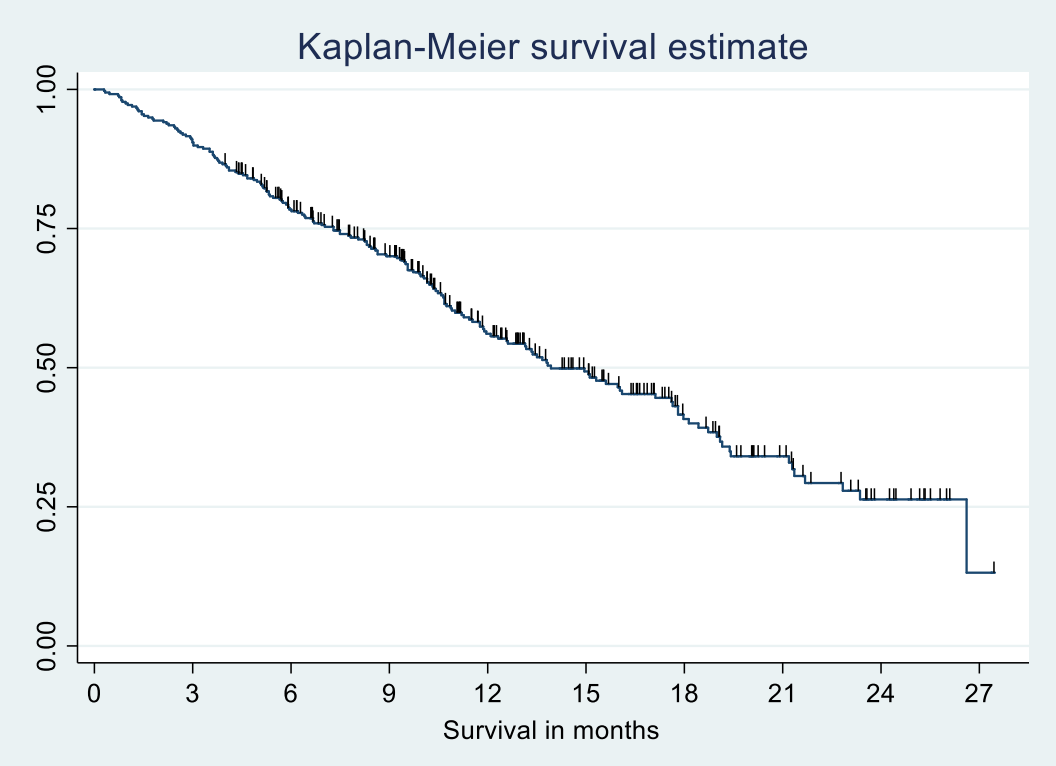


Table 8 and 9 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 28 months, all patients were traced on 15 January 2019.

Table 8: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-28	3 -28	6 -28	9 -28	12-28	15 -28	18-28	21-28	24-28	28
Number at risk	357	323	259	205	131	91	52	31	13	1

Table 9 shows that for all patients who received treatment, 177 were still alive (censored) at the date of follow-up and 180 had died (events).

Table 9: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	0-28	3 -28	6 -28	9 -28	12-28	15 -28	18-28	21-28	24-28	28
Censored	177	177	155	127	89	63	37	24	12	1
Events	180	146	104	78	42	28	15	7	1	0

Sensitivity analyses

Treatment duration

Sensitivity analyses was carried out on a smaller cohort to allow at least 6 months follow-up in SACT, 278 patients (78%) were included in these analyses. To identify the cohort CDF applications were limited from 4 October 2016 to 30 March 2018 and SACT activity was followed up to the 30 September 2018. The median follow-up time in SACT was 252 days.

The Kaplan-Meier curve for ongoing treatment is shown in figure 5. The median treatment duration for patients in this cohort was 9 months [95% CI: 8.3, 10.1] (N=278).

Figure 5: Kaplan-Meier treatment duration (N=278)

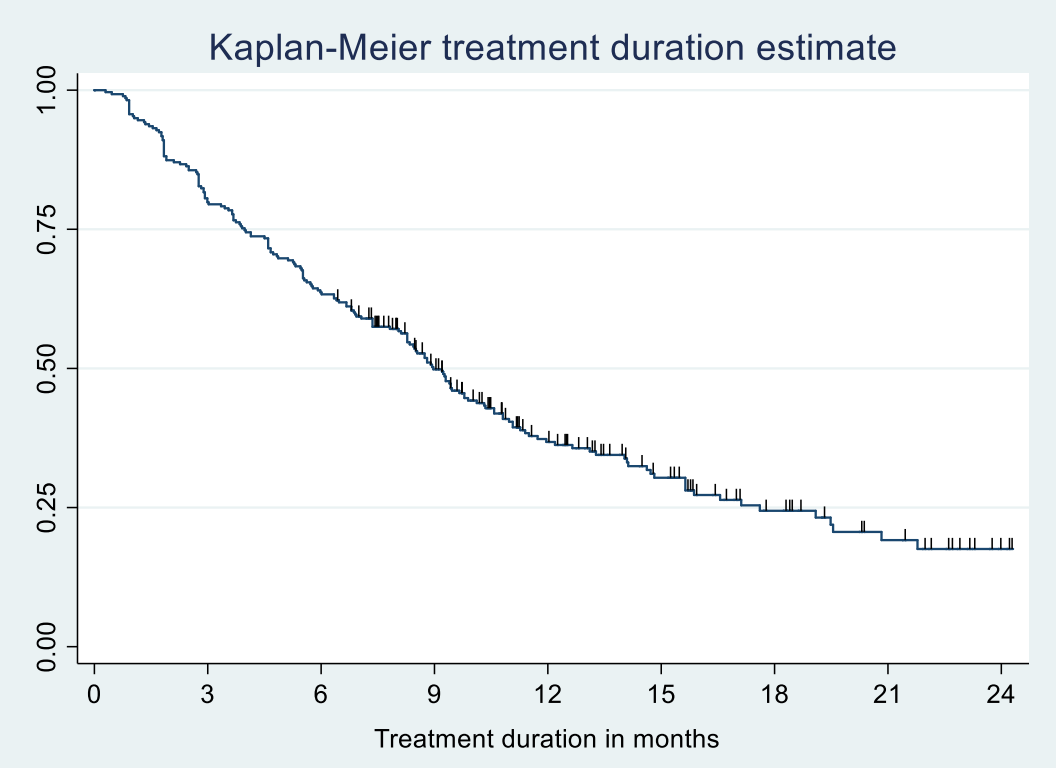


Table 10 and 11 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for treatment duration was 24 months. The minimum follow-up was 6 months.

Table 10: Number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0 - 24	3 - 24	6 - 24	9 - 24	12 - 24	15-24	18-24	21-24	24
Number at risk	278	222	177	119	68	43	24	13	2

Table 11 shows that for all patients who received treatment, 91 were still on treatment (censored) at the date of follow-up and 187 had ended treatment (events).

Table 11: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored).

Time intervals (months)	0 - 24	3 - 24	6 - 24	9 - 24	12 - 24	15-24	18-24	21-24	24
Censored	91	91	91	69	46	31	19	12	2
Events	187	131	86	50	22	12	5	1	0

Overall survival

330 patients (92%) were included in the survival analyses with all patients having a minimum follow-up of 6 months. Follow up continued from treatment start date to date of tracing for vital status (15 January 2019). CDF applications that have been included have been limited from 4 October 2016 to 15 July 2018.

Figure 6 provides the Kaplan-Meier curve for OS, censored at 15 January 2019. The median survival was 13.8 months [95% CI: 12.0, 17.6] (N=330).

Figure 6: Kaplan-Meier survival plot (N=330)

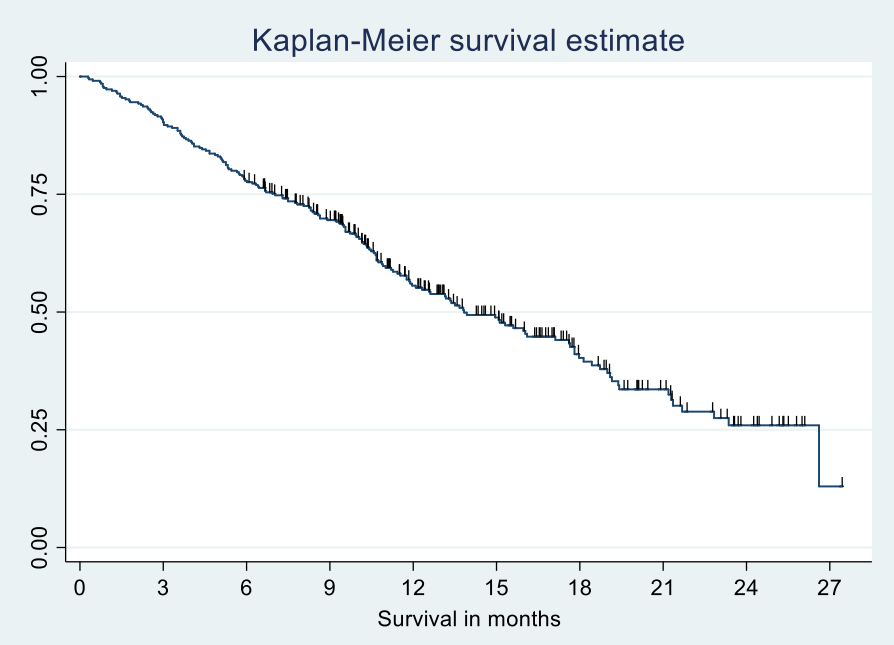


Table 12 and 13 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The follow-up period for survival was 28 months, all patients were traced on 15 January 2019.

Table 12: Includes the number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0-28	3-28	6-28	9-28	12-28	15-28	18-28	21-28	24-28	28
Number at risk	330	298	256	204	130	90	51	31	13	1

Table 13 shows that for all patients who received treatment, 153 were still alive (censored) at the date of follow-up and 177 had died (events).

Table 13: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints.

Time intervals (months)	0-28	3-28	6-28	9-28	12-28	15-28	18-28	21-28	24-28	28
Censored	153	153	152	126	88	62	36	24	12	1
Events	177	145	104	78	42	28	15	7	1	0

Conclusions

371 unique CDF (Blueteq) applications were made for osimertinib for the treatment of locally-advanced or metastatic EGFR and T790M mutation-positive NSCLC in the reporting period (4 October 2016 and 4 September 2018). All patients were either reported to the SACT dataset or the team at PHE could confirm with the trust responsible for the CDF application that the patient did not receive treatment. For the 357 patients receiving treatment in the approved indication, SACT ascertainment was 100%.

Patient characteristics from the SACT dataset show that proportionally more women received osimertinib treatment compared to males (68% female, 32% male). Most of the cohort was aged between 50 and 79 years (82%) and 84% of patients had a performance status between 0 and 1 at the start of their regimen.

At the end of the data collection period, 208 patients were identified as no longer receiving treatment. Of these, 100% (N=208) patients had an outcome submitted by the treating trust, which detailed the reason why a patient ended their treatment. 63% (N=130) of patients had stopped treatment due to disease progression, 3% (N=6) had stopped treatment due to toxicity, 5% (N=10) patients chose to end their treatment, 18% (N=38) of patients died (not on treatment) and 12% (N=24) of patients died on treatment.

The median treatment duration was 9 months [95% CI: 8.3, 10.1] (274 days). The median follow-up was 196 days and the maximum follow-up was 24 months (730 days).

The median OS was 13.9 months [95% CI: 12.1, 17.6] (423 days). The minimum follow-up was 4 months, the maximum follow-up was 28 months (852 days).

Sensitivity analyses were carried out to evaluate a cohort for which all patients had a minimum follow-up of 6 months. Results for this cohort showed no difference in treatment duration (full cohort and limited cohort median treatment duration = 9 months) and only a very slight difference in survival (full cohort OS = 13.9 months; limited cohort OS = 13.8 months). This difference was not statistically significant.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer [ID1577]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Shobhit Baijal**
2. Name of organisation	**University Hospital Birmingham NHS Trust**

3. Job title or position	**Consultant Medical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of the treatment is to: 1. Prevent progression and hence ultimately improve overall survival for patients with the condition. 2. By reducing the burden of the cancer and having greater efficacy against brain metastases, it will also improve the quality of life of patients with the condition.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	An improvement of greater than 3 months progression free survival compared with the standard of care
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is definitely an unmet need for EGFR mutation positive patients who have progressed on their first line (first or second generation) EGFR TKI. The default option is chemotherapy, which carries poor tolerance and clinical outcomes. For those patients that acquire the T790M mutation Osimertinib is a far superior therapy option compared with chemotherapy – as proven by the AURA 3 clinical trial
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Currently we have access to Osimertinib via the CDF. Outside of access to Osimertinib patients would be treated with systemic anti-cancer therapy, which carries very poor tolerance and response rates / progression free survival.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	All major Oncology bodies (ESMO, ASCO, NCCN) recommend the use of Osimertinib for T790M positive NSCLC
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	This pathway is very well defined and established. Patients that are progressing on their first line EGFR TKI are tested (liquid and or tissue biopsy) for the presence of the T790M mutation. Those that test positive are a candidate for treatment with Osimertinib.
• What impact would the technology have on the current pathway of care?	Without access to 2nd line Osimertinib for T790M positive patients this would almost half the overall survival of patients and also impact on their quality of life due to the burden / volume of their malignancy
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It would continue to be utilised as per the CDF usage

• How does healthcare resource use differ between the technology and current care?	Osimertinib is an oral medication which is taken by the patients at home. Overall it is well tolerated and patients are rarely admitted with toxicities. The alternative option is systemic anti-cancer treatment, which requires increased resources (day unit and chemotherapy nursing time). It also carries a higher toxicity profiles with the potential of hospital admissions.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Advanced EGFR positive NSCLC in patients who have progressed on their first line TKI and acquired the T790M mutation
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	n/a
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – as per above based on improved survival outcomes and quality of life for patients
• Do you expect the technology to increase length of life more than current care?	Yes – based on the AURA 3 clinical trial data

• Do you expect the technology to increase health-related quality of life more than current care?	Yes – based on the AURA 3 clinical trial data
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As per the drug's indication – it would only be for patients who were T790M positive
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Osimeritnib would be easier to use than standard of care as it is an oral medication, which patients would take at home as opposed to the alternative treatment which would be systemic anti-cancer treatment (delivered on a day unit).

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The patient will have to have confirmed T790M positivity (liquid or tissue) to start the treatment. Treatment would be discontinued on radiological and clinical progression, which will require CT imaging.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes – the identification of the T790M mutation and the proven efficacy of Osimertinib against this mutation is cutting edge and illustrates the evolution / resistance mechanism in the EGFR landscape and how effective a 3rd generation EGFR TKI is against it.

impact on health-related benefits and how might it improve the way that current need is met?	The efficacy over chemotherapy is clearly illustrated by the AURA 3 clinical trial.
• Is the technology a 'step-change' in the management of the condition?	The technology is a landmark development in the management of this condition.
• Does the use of the technology address any particular unmet need of the patient population?	Yes It provides an effective / life prolonging treatment for patients that acquire the T790M mutation following first line treatment with anti-EGFR TKI.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The treatment is overall very well tolerated as per the clinical trial data and my personal experience. It is much better tolerated than the alternative treatment option (chemotherapy). Also patients often respond early which reduces cancer related symptoms and hence improves quality of life.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Progression free survival and objective response rate
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
20. Are you aware of any relevant evidence that might	

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA416]?	
22. How do data on real-world experience compare with the trial data?	Real world experience is comparable with the trial data
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	n/a

23b. Consider whether these issues are different from issues with current care and why.	n/a
Topic-specific questions	
24. What overall survival would you expect for people who are given osimertinib?	27 months
25. What overall survival would you expect for people who are given platinum-doublet chemotherapy?	16 months
Key messages	

26. In up to 5 bullet points, please summarise the key messages of your statement.

- Osimertinib is highly effective in T790M positive EGFR NSCLC
- Significantly more effective than chemotherapy
- Well tolerated and convenient to take as oral medication
- High response rates and good CNS penetration translates into good quality of life for patients with high volume / symptomatic disease
- My personal experience matches the trial data – without this drug available there will be a high unmet need for this patient population

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NICE National Institute for Health and Care Excellence

Patient expert statement

Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer (CDF Review of TA416) [ID1577]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Jenny Abbott**

2. Are you (please tick all that apply):	**X** a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	EGFR Positive UK
4. Did your nominating organisation submit a submission?	**X** yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	**X** I have personal experience of the condition **X** I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I was diagnosed with EGFR positive lung cancer in February 2017 - a fit and healthy 54 year old mother with three children, age seventeen, fifteen, and thirteen at the time of my diagnosis. I have never smoked, and on Saturday went for my usual run round my local park, feeling fine. On Tuesday, I found myself in my local A&E with shortness of breath and the following day, I was told I had stage IV NSCLC which later tested positive for an EGFR mutation. I was initially treated with afatanib which worked for seven months and I then tested positive for T790M which meant I was able to have osimertinib as a second line treatment. This stopped working effectively for me after nine months and after continuing on osimertinib for a further two months, I am now being treated with chemotherapy. For my children, the impact of knowing that they will lose their mother is profound and, for me it is the single most difficult thing about my illness. I cannot bear the idea of leaving them and the knowledge that they will have to navigate such grief and loss at an early age is something that I think about every day,

	whilst also trying to maintain as normal a life as possible for them. Osimertinib as a second line treatment for T790M has given us a year of that normal life, another year for them to grow and mature, another year for me to be their mother, another year in which my husband and I have been able to share the joys and challenges of being parents to three teenagers. One of the greatest benefits of osimertinib, is that the side effects have been minimal. On afatanib, I lost a significant amount of my hair, often had diarrhoea, and also rashes and sores on my face and in my nose. It became impossible for me to watch my sports mad sons play football (no adequate toilet facilities at football pitches) and a simple shopping trip with my daughter was fraught with worries about whether I would be able to find a loo in time. I also looked different and I know this pained my children, although they were never anything but encouraging and reassuring. On osimertinib, I became a 'normal' mum once again - able to do everything, looking as I always did. We have been on holiday, we have had mother and daughter trips out, I have been to see my sons play football again. We have existed almost as we did before. This time has been precious - both the amount of time it has given us but also the quality of that time. My daughter has navigated her first year of university and her panic about leaving me subsided knowing that I was well, more university applications are underway, GCSE subjects have been chosen and the odd football trophy won - the small milestones of everyday life which are no longer taken for granted but for me bring the joy of knowing I was there, I witnessed and I helped. And perhaps even more importantly are all the very ordinary moments we have shared - cups of tea in the kitchen, the cuddles on the sofa, the family jokes, the walks in the park, the drive to football practice listening to music and chatting, the favourite birthday cake which was made by me for another year. A whole family suffers when a parent has cancer. A drug which offers significant life extension is invaluable, but one which also offers my children, and the children and families of other lung cancer patients, the chance to be normal again is priceless. The mental health benefits for the whole family are profound - we do not deny the reality of the situation, but we have been able to live well with it for this last year. For me, for my husband and for our children, chemotherapy brings new challenges and another shift in our sense of time and what it means. We are learning to adapt again but I miss my daily pill and all that it represented.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	There are not enough options for NSCLC patients with an EGFR mutation - many of whom are younger, never-smokers who need to work and have dependent children.
10. Is there an unmet need for patients with this condition?	
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Significant life extension, effective CNS control, and minimal side effects compared to other TKIs. Easy to take and cuts down on hospital visits and appointments.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	None

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It is important to ensure when considering this technology that all EGFR patients who progress on first or second generation TKIs have the opportunity to have further tissue or liquid biopsies to ensure that they have the best chance of discovering if T790M is present.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	There are currently no other treatment options for EGFR T790M mutation positive lung cancer apart from chemotherapy which has significant quality of life impact for patients and does not over the survival benefits of this technology.

Key messages
17. In up to 5 bullet points, please summarise the key messages of your statement: ● This technology offers overall survival benefit ● It also offers meaningful and significant quality of life benefit ● It has significant impact on mental health and well- being of patients and their family members. ● It offers proven CNS control and benefit. ● It is a daily tablet which is easy to take and cuts down on hospital appointments.

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NHS England submission on the NICE re-appraisal of CDF osimertinib in the 2nd line treatment of EGFR T790M mutation positive locally advanced/metastatic non small cell lung cancer (NSCLC)

The paragraph below in this colour is commercial in confidence

1. Osimertinib has been in the CDF since October 2016. PHE and its SACT team have analysed the outcomes of 357 consecutive patients who received CDF osimertinib for the 2nd line treatment of EGFR T790M mutated NSCLC. There are CDF treatment duration and overall survival outcomes for all of these 357 patients, this reflecting a very substantial series of real world use in the NHS in England. NHS England pays tribute to PHE and its SACT team for such an achievement in this complete data collection across all the treating hospitals in England.
2. The median treatment duration was 9.0 months in the CDF which is similar to both the 8.6 month figure in the AURA 3 trial and the median progression free survival figure of 10.1 months in AURA 3, the latter two figures reported in NEJM 2017; 376: 629-640. Many if not most CDF patients will have received osimertinib for a significant period after disease progression whereas osimertinib was stopped at disease progression in AURA 3. Reasons for NHS treatment beyond disease progression are multiple: less frequent monitoring CT scans, the continued symptomatic benefit of treatment despite RECIST disease progression, continuing systemic control of the disease at a time of progression of brain metastases amenable to radiotherapy and overall and continuing systemic control of the disease at a time when there is disease progression at one site which is amenable to radiotherapy. Committee D will be familiar with these reasons. NHS England would conclude that treatment duration in AURA 3 would have been longer than in the real world of the NHS had a similar NHS clinical practice been allowed in the trial.
3. The median survival in the CDF series of 357 patients was 13.9 months, a figure in stark contrast to the 26.8 month figure in the 279 patients treated with osimertinib in the AURA 3 study.
4. The demographic types of the patients in the CDF and AURA 3 groups have some similarities. The proportions of females treated are very similar (68% in the CDF, 64% in AURA 3). All patients in both sets of patients had EGFR T790M mutated NSCLC and all received osimertinib as second line systemic therapy after 1st line EGFR TKI therapy. All patients in AURA 3 were of ECOG performance score of 0 or 1 and a CDF requirement on entry was also to have a score of 0 or 1.
5. The age analyses were performed differently in the two groups but it is clear that the CDF population was modestly older. In the CDF, 40% of patients were aged 70 or more and 71% were aged 60 or more. In AURA 3, the median age was 62 years and 15% were aged 75 years or more.
6. Even though there was no analysis by ethnicity in the CDF group, the biggest difference between the two populations lies in the fact that 65% of AURA 3 patients

were of Asian origin. Whatever the proportion of patients of Asian ethnic origin in the CDF group, the figure will be nowhere near the figure of 65%. That this ethnicity factor is important lies is evidence in the subgroup analyses for PFS for the Asian population in AURA 3 which show a HR of 0.32 whereas the figure for the non-Asian population is 0.48, suggesting the potential for a greater treatment benefit for osimertinib in Asian patients. This suggests that the benefit of osimertinib in this indication would be potentially less than that seen in AURA 3.

7. Another difference between the CDF and AURA 3 groups is likely to be the proportion of patients with CNS metastases at the start of treatment. In AURA 3, 34% of patients had CNS metastases prior to trial entry, these having been identified by scanning at baseline, medical history, and/or prior surgery and/or prior radiotherapy to CNS metastases. In the CDF group, there was no record of CNS metastasis at the start of osimertinib, nor was there any requirement for brain scanning at that time in patients without CNS symptoms. NHS England concludes that the incidence and morbidity of brain metastases could explain part of the disparity between the overall survival durations in the CDF versus the AURA 3 trial.
8. A further difference between the two groups is likely to be the type of 1st line therapy. 94% of patients in AURA 3 received 1st line treatment with a 1st generation EGFR TKI (erlotinib, gefitinib). Although the CDF figures for 1st line treatment were not recorded, afatanib (a 2nd generation EGFR TKI) was recommended by NICE in 2014 and has since become the dominant EGFR TKI in the NHS in the 1st line treatment of EGFR mutated NSCLC. As a consequence, CDF osimertinib would have been most used after disease progression on afatinib. How important this might be in explaining the difference between the CDF and AURA 3 overall survivals is not known to NHS England.
9. NHS England notes the difference between the median overall survival and the median treatment duration in the CDF and AURA 3 groups. For the CDF, this difference is 4.9 months. For the AURA 3 trial patients, this difference (using the NEJM 2017 figure for median treatment duration) is 18.2months. Even when the median PFS is subtracted from the overall survival duration in AURA 3, the post progression survival figure is 16.6 months in AURA 3. The post-treatment survival durations therefore seem very different in the CDF versus AURA 3.
10. Given the above CDF real world NHS data in a very large cohort of patients, NHS England therefore has concerns that the benefits for 2nd line osimertinib based on modelling of AURA 3 trial data may not be realised in practice and is therefore optimistic.
11. [redacted]

[redacted]

Prof Peter Clark

National Clinical lead for the Cancer Drugs Fund

NHS England

February 2020

Cancer Drugs Fund Review

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer [1559]

Cancer Drugs Fund update of TA416

This report was commissioned by the NIHR Systematic Reviews Programme as project number 129027

Completed 29 November 2019

DOES CONTAIN CIC/AIC

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title:	Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer [ID1577] (Cancer Drug Fund update of TA416)
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Contributions of authors:

Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Rachel Houten	Critical appraisal of the economic evidence
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
James Mahon	Critical appraisal of the economic evidence
Marty Chaplin	Critical appraisal of the statistical evidence

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LIST OF ABBREVIATIONS

AC	Appraisal Committee
AE	Adverse event
AF	Acceleration factor
AUC	Area under the curve
AURA	Clinical programme of trials assessing the clinical effectiveness of osimertinib
BSA	Body surface area
CDF	Cancer Drugs Fund
CI	Confidence interval
CS	Company submission
ctDNA	circulating tumour DNA
DC	Data-cut
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EGFR (-TKI)	Epidermal growth factor receptor (tyrosine kinase inhibitor)
EGFRm+	EGFR mutation-positive
EMA	European Medicines Agency
EORTC	European Organisation for the Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions Questionnaire
ERG	Evidence Review Group
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
IMPRESS	Iressa Mutation-Positive Multicentre Treatment Beyond Progression Study
IPCW	Inverse Probability of Censoring Weighting
IPD	Individual patient data
K-M	Kaplan-Meier
MAIC	Matching-adjusted indirect comparison
NICE	National Institute of Health and Care Excellence
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressed disease
PDC	Platinum doublet chemotherapy
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazards
PHE	Public Health England
PS	Performance status
PSS	Personal and Social Services
QALY	Quality adjusted life year
RPFSTM	Rank Preserving Failure Structural Time Model
SACT	Systemic Anti-Cancer Therapy
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
T790M	Secondary mutation of the EGFR
ToE	Terms of Engagement
TTD	Time to treatment discontinuation

1 EXECUTIVE SUMMARY

In October 2016, the outcome of National Institute for Health and Care Excellence (NICE) Technology Appraisal TA416 was that osimertinib was recommended as an option for use within the Cancer Drugs Fund (CDF) for treating locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) in adults whose disease had progressed after first-line treatment with an EGFR-tyrosine kinase inhibitor (TKI).

To inform TA416, the company provided evidence from the AURAext and AURA2 trials. These two single-arm trials were designed to assess the clinical effectiveness of osimertinib in patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who had received treatment with an EGFR-TKI prior to recruitment. Patients in the AURAext and AURA2 studies had received between 1 and 14 prior anti-cancer treatments, including an EGFR-TKI. The data used to inform the comparison of the effectiveness of osimertinib versus platinum doublet chemotherapy (PDC) were obtained from a subgroup of patients included in the control arm of the IMPRESS trial whose tumours were identified retrospectively as having the EGFR T790M mutation. These patients had received placebo+pemetrexed+cisplatin.

The availability of final overall survival (OS) data from the AURA3 trial (osimertinib versus PDC) has triggered this review of the evidence. To inform this CDF review, as well as updated AURAext, AURA2 and AURA3 trial results, the company has also provided results from two sets of data extracted from the Systemic Anti-Cancer Therapy (SACT) dataset: (i) patients treated with osimertinib via the CDF and (ii) patients who received an EGFR-TKI as first-line therapy.

This Evidence Review Group (ERG) report focuses on the key issues outlined in the final Terms of Engagement (ToE) document issued by NICE. The ToE, although not binding, outlines NICE's expectations relating to the content of the company submission (CS) for the CDF review.

1.1 Population

The NICE Appraisal Committee's (AC) preferred population was adults with locally advanced or metastatic EGFR T790M mutation-positive NSCLC. This matches the population recruited to the AURAext and AURA2 trials. However, the population recruited to the AURA3 trial was a subset of this population, namely patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease had progressed after first-line EGFR-TKI therapy.

The AURA3 trial population matches the population described in the company Managed Access Agreement.

1.2 Comparators

The NICE AC's preferred comparator was PDC.

The AURAext and AURA2 trials are single-arm studies. The company generated comparator data through the use of a matching-adjusted indirect comparison (MAIC). The initial step of this technique involved matching baseline characteristics of patients in the AURAext and AURA2 trials with those of patients in the comparator arm of the IMPRESS trial (placebo+pemetrexed+cisplatin).

Direct evidence for the effectiveness of osimertinib versus PDC was available from the AURA3 trial (osimertinib versus pemetrexed+carboplatin or pemetrexed+cisplatin).

1.3 Generalisability

The NICE AC concluded that the AURAext and AURA2 trials were broadly generalisable to clinical practice.

The ERG considers that whilst patient characteristics and the magnitude of key outcomes from all three AURA trials are similar, the generalisability of this evidence to clinical practice is unclear because of differences between trial and Systemic Anti-Cancer Therapy (SACT) dataset survival results, the latter being considerably lower than trial results. The reasons for the large discrepancies are unknown.

1.4 Overall survival

The NICE AC concluded that whilst it was reasonable to pool data from the AURAext and AURA2 trials, the data were too immature to robustly estimate the OS advantage of treatment with osimertinib versus PDC.

The latest pooled AURAext/AURA2 trial and AURA3 trial median OS results for patients receiving osimertinib as a second-line treatment are similar (median=26.5 months and 26.8 months respectively). Results from the AURA3 trial show that, for the comparison of treatment with osimertinib versus PDC, OS is not statistically significantly different. However, patients randomised to the PDC arm of the AURA3 trial were permitted to switch treatments after disease progression and 71% of patients randomised to the PDC arm received osimertinib in this way (i.e., crossed over). As treatment with osimertinib is not currently recommended by NICE (or available via the CDF) for use as a >second-line therapy, use of ostimertinib as a third-line treatment does not reflect current NHS practice. The company considered three

different approaches to removing the effect of crossover on OS estimates for patients randomised to receive PDC and concluded that the RPFSTM method was the most appropriate. The ERG considers that it is unclear which of these three methods would produce the most valid estimates of treatment effect and highlights the very high level of patient crossover (71%) in the AURA3 trial. The company chose to generate results using six variants of the Rank Preserving Structural Failure Time Model (RPSFTM). The hazard ratio results generated by these methods ranged from [redacted]. It is not known whether one of the RPFSTM crossover adjustment methods provides more realistic results than any of the others.

The company's AURA3 trial median crossover adjusted OS estimates for patients receiving PDC ranged from [redacted] months to [redacted] months. In contrast, median OS for patients from the IMPRESS trial who were matched with patients in the AURAext and AURA2 trials was 14.1 months and the median OS calculated from SACT data collected from NHS patients who had received initial treatment with an EGFR-TKI and went on to receive a subsequent anti-cancer treatment was 8.31 months.

1.5 Summary of key issues in clinical effectiveness evidence

The AURA3 trial provides direct evidence of the effectiveness of osimertinib versus PDC for patients who have only previously been treated with an EGFR-TKI. Survival results from the AURA3 trial support results from the pooled AURAext/2 dataset. Nearly three-quarters (71%) of patients in the PDC arm of the AURA3 trial crossed over to receive osimertinib on progression. The company considers that the RPSFTM is the most appropriate method to use to adjust for the effect of crossover. The ERG considers it is not possible to choose a 'best' method of crossover adjustment.The company has presented crossover adjusted results generated by six variants of the RPFSTM. All methods generate hazard ratios with [redacted]. It is not possible to determine which of the RPFSTM methods generates the most realistic results. The company's PDC base case median crossover adjusted OS result was more optimistic that results from the company's adjusted indirect comparison or from the SACT data (medians: [redacted]14.1 and 8.31 months respectively). These differences cast uncertainty on the generalisability of results from the three AURA trials to NHS clinical practice.

1.6 Summary of key issues in cost effectiveness evidence

Two models are included in the CDF Review CS (Model A and Model B). The basic structure of Models A and B and the model submitted as part of the TA416 CS were the same. Model A differed from that submitted as part of the TA416 CS only in that it included estimates of OS, PFS and TTD from the most up to date pooled AURAext/2 data. The key differences between Model A and Model B were that Model A was populated with OS, PFS and TTD estimates from the most up to date pooled AURAext/2 dataset whilst Model B was populated with OS, PFS and TTD estimates from the most up to date AURA3 trial data.

During TA416 the company concluded that the most likely utility estimates fell between optimistic values used by the company (derived from data collected during the AURA2 trial) and less optimistic values derived from data collected during the LUME-Lung 1 trial. Health-related quality of life data were collected as part of the AURA3 trial. Utility values derived from these data are very similar to the AURA2 values.

1.7 Summary of exploratory and sensitivity analysis undertaken by the ERG

Following discussion with the NICE technical team, the ERG created a hybrid model (Model A/B) which meets the ToE for this review better than either Model A or Model B. Model A/B has been constructed by replacing the OS, PFS and TTD data in Model A with OS, PFS, TTD data from the AURA3 trial (Model B). Using the CAA price for treatment with osimertinib and list prices for pemetrexed and cisplatin, the ERG has made four amendments to Model A/B, namely revised OS, PFS and TTD estimates (generated using AURA3 trial data) and use of the LUME-Lung 1 trial utility values. The ERG has also presented results from two scenarios:

- Scenario 1: changes to OS, PFS and TTD
- Scenario 2: changes to OS, PFS, TTD and using LUME-Lung 1 trial[1] utility values.

Model A/B base case results and results from these two scenarios are provided in the table below.

Exploratory analyses undertaken by the ERG

ERG amendment/scenario	Incremental			*ICER*	
	Cost	Life years	QALYs	£/QALY	Change from base case
A. Model A/B base case	£68,792	1.030	0.817	£84,209	
Scenario 1: R1)+R2)+R3)	£66,011	1.106	0.897	£73,565	-£10,644
Scenario 2: R1)+R2)+R3)+R4)	£66,011	1.106	0.719	£91,812	£7,602

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

1.8 End of Life

The NICE End of Life criteria are:

- treatment is indicated for patients with a short life expectancy, normally less than 24 months and
- there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The company's AURA3 crossover adjusted median OS estimates for patients receiving PDC ranged from [redacted] months to [redacted] months. The company's and ERG mean estimates of OS for patients receiving PDC from their modelling of OS from AURA3 trial data are [redacted] and [redacted] months respectively. The ERG therefore considers that the short life expectancy criterion is met.

A comparison of the company's AURA3 trial crossover adjusted median OS results show the difference between treatment with osimertinib and PDC to be a minimum of [redacted] months and a maximum of [redacted] months. From the company's modelling of AURA3 data, mean estimates of OS are [redacted] months for osimertinib and [redacted] months for PDC. The ERG's revised mean estimates of OS are [redacted] months for osimertinib and [redacted] months for PDC. The ERG therefore considers that the life extension criterion is met.

2 BACKGROUND

2.1 Introduction

In October 2016, osimertinib was recommended by the National Institute for Health and Care Excellence (NICE) as an option for use within the Cancer Drugs Fund (CDF) for treating locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) in adults whose disease had progressed:

- after first-line treatment with an EGFR-tyrosine kinase inhibitor (TKI) and
- if the conditions in the Managed Access Agreement (MAA)[2] for osimertinib were followed.

It is stated within the CDF review CS (Appendix 3),[3] that representatives from NHS England, NICE, Public Health England (PHE) and the company (AstraZeneca) formed a working group to agree the:

- eligibility criteria for patient access to osimertinib through the CDF
- the real-world data to be collected and analysed to support the CDF review
- CDF entry and exit dates.

The availability of final overall survival (OS) data from the AURA3 trial[3] has triggered this review of the evidence. This Evidence Review Group (ERG) report focuses on the key issues outlined in the final Terms of Engagement (ToE) document[4] issued by NICE. The ToE,[4] although not binding, outlines NICE's expectations relating to the content of the company submission (CS) for the CDF review.

2.2 Osimertinib

Key facts about osimertinib:

- Indicated for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC
- Testing to confirm the presence of the EGFR T790M mutation is necessary prior to treatment initiation
- Approval by the European Medicines Agency (EMA) for the treatment of adult patients with locally advanced or metastatic EGFR T790 mutation-positive NSCLC was granted on 17 December 2015[5]
- Available as 40mg or 80mg tablets
- The recommended dose is 80mg once a day until disease progression or unacceptable toxicity
- Available to the NHS at a discounted price via a Commercial Access Agreement (CAA).[2]

2.3 Testing for the EGFR T790M mutation in the NHS

It is necessary to confirm the presence of the EGFR T790M mutation prior to treatment with osimertinib. EGFR mutation status can be confirmed by two types of test: (i) using either tumour deoxyribonucleic acid (DNA), derived from a tissue sample, or (ii) circulating tumour DNA (ctDNA), obtained from a plasma sample. Clinical advice to the ERG is that plasma testing for T790M mutations at relapse is now widely available but concerns remain about false negative results. A number of different tests are available and the technology continues to evolve. However, in the event of a negative plasma DNA test, not all patients are suitable for rebiopsy on account of tumour location or patient fitness.

3 THE CLINICAL DECISION PROBLEM

The NICE AC's preferred clinical assumptions (as set out in the Terms of Engagement document)[4] are presented in Table 1. Further information relating to each assumption is provided in the text following the table.

Table 1 NICE Appraisal Committee's preferred clinical assumptions

Area	Summary of NICE Appraisal Committee's preferred assumptions
Population	*Adults with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.*
Comparators	*Platinum doublet chemotherapy was the most relevant comparator for this appraisal.*
Generalisability	*The trials used as the basis for evaluating the efficacy of osimertinib in people with EGFR T790M mutation-positive NSCLC that has progressed on a previous TKI were broadly generalisable to clinical practice.*
Overall survival	*Pooling the results for the two AURA trials was reasonable given that the studies were very similar regarding baseline characteristics.* *The available data were too immature to robustly estimate the overall survival advantage of osimertinib compared with platinum doublet chemotherapy.*

EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer; OS=overall survival; TKI=tyrosine kinase inhibitor
Source: NICE 2018[4]

3.1 Population

Box 1 NICE Appraisal Committee's preferred assumption: population

The NICE AC considered that the population should be adults with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

Source: NICE 2018[4]

The NICE AC's preferred population matches the population recruited to the AURAext and AURA2 trials.[6] However, the population recruited to the AURA3 trial was a subset of this population, namely patients with locally advanced or metastatic NSCLC whose disease had progressed after first-line EGFR-TKI therapy and who tested positive for an EGFR mutation with the T790M variant. The ERG notes that the population described in the MAA[2] is the same population as that recruited to the AURA3 trial.

The baseline characteristics of the population recruited to the AURA3 trial are similar to those of patients who were recruited to the AURAext and AURA2 trials (

Table 2). The ERG highlights that:

- Clinical advice to the ERG is that patients with EGFR mutation-positive (EGFRm+) disease who are treated in the NHS are typically aged between 65 years and 70 years and the majority are of Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 1 or 2.
    - Patients participating in the AURA trials are younger (median: 62-63 years) and fitter (ECOG PS 0 or 1) than EGFRm+ patients treated in the NHS.
    - Patients participating in the IMPRESS trial are also younger (mean age of 58.1 years) and fitter (ECOG PS 0 or 1) than EGFRm+ patients treated in the NHS.
- Whilst all patients recruited to the AURA3 trial received osimertinib in the second-line setting (after an EGFR-TKI), 12.4% of patients recruited to the AURAext and AURA2 studies had received more than five lines of prior treatment. Clinical advice to the ERG is that the majority of patients treated in the NHS are not well enough to tolerate more than one or two chemotherapy treatments after a first-line EGFR-TKI.

Table 2 Baseline characteristics of patients participating in the three AURA trials

Demographic characteristic		Trial			
		Pooled AURAext/2		AURA3	
Indication		≥Second-line	Second-line	Second-line	
Treatment		Osimertinib	Osimertinib	Osimertinib	PDC
Number of patients		411	92	279	140
Age (years)	Mean (SD)	62.2 (11)	61.8 (11)	61.5 (12)	62 (12)
	Median (min-max)	63 (35-89)	60 (36-89)	62 (25-85)	63 (20-90)
	% ≥65 years	187 (46)	36 (39)	114 (41)	63 (45)
Sex n (%)	Male	132 (32)	32 (35)	107 (38)	43 (31)
	Female	279 (68)	60 (65)	172 (62)	97 (69)
Smoking n (%)	Never	284 (69)	63 (69)	189 (68)	94 (67)
	Ever	114 (28)	29 (31)	76 (27)	38 (27)
	Current	7 (2)	0 (0)	14 (5)	8 (6)
EGFR mutation n (%)	Exon 19 deletion	279 (68)	67 (73)	191 (68)	87 (62)
	L858R in exon 21	118 (29)	23 (25)	83 (30)	45 (32)
	Other	14 (3)	NR	6 (<3)	5 (3)
ECOG / WHO PS n (%)	0	152 (37)	43 (47)	103 (37)	56 (40)
	1	258 (63)	49 (53)	117 (63)	84 (60)
	2	1 (<1)	0 (0)	0 (0%)	0 (0)
	3	0 (0%)	0 (0)	0 (0%)	0 (0)
	4	0 (0%)	0 (0)	0 (0%)	0 (0)
	0–1	410 (100)	92 (100)	279 (100)	140 (100)
	2–4	1 (<1)	0 (0)	61.5 (12)	0 (0)
Metastatic at baseline n (%)		395 (96)	86 (94)	266 (95)	138 (99)
Brain metastatic at baseline n (%)		166 (40)	23 (25)	93 (33)	51 (36)
Race n (%)	White	149 (36)	36 (39)	89 (32)	45 (32)
	Asian	247 (60)	55 (60)	182 (65)	92 (66)
	Other	15 (4)	1 (1)	8 (3)	3 (2)

ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; NR=not reported; PDC=platinum doublet chemotherapy; PS=performance status; SD=standard deviation; TKI=tyrosine kinase inhibitor
Source: Company response to clarification[7]

3.2 Comparators

Box 2 Appraisal Committee's preferred assumption: comparators

The NICE AC considered that platinum doublet chemotherapy was the most relevant comparator.

Source: NICE 2018[4]

The AURAext and AURA2 trials are single-arm studies. To generate comparator data for TA416,[6] the company carried out a matching-adjusted indirect comparison (MAIC 1). This technique included matching baseline characteristics of patients recruited to the control arm

of the IMPRESS trial[8] who were identified retrospectively as having the EGFR T790M mutation with those of patients recruited to the AURAext and AURA2 trials. The IMPRESS trial was designed to compare the efficacy of gefitinib+pemetrexed+cisplatin versus placebo+pemetrexed+cisplatin (placebo+PDC). MAIC 1 included data from 129 patients recruited to the AURAext and AURA2 trials and a maximum of 61 patients recruited to the IMPRESS trial.

As part of their response[9] to the NICE Appraisal Consultation Document,[10] the company provided results from a MAIC that only included data relating to patients receiving second-line treatment (henceforth referred to as MAIC 2). Following cohort balancing, MAIC 2 included data from 92 patients treated with osimertinib and 53 patients treated with PDC. The ERG's primary concerns relating to MAIC 1[11] and MAIC 2[12] were the small numbers of patients and the immaturity of the pooled AURAext/2 data (data-cut [DC] 04).

The company has submitted MAIC 3 (an updated MAIC 2) as part of the CDF Review CS. MAIC 3 includes mature pooled AURAext/2 data (DC05, 60.9% of OS events had occurred). MAIC 2 and MAIC 3 OS results are provided in Table 3. The ERG considers that the maturity of the data renders results from MAIC 3 more credible than those from MAIC 2; however, confidence in the generalisability of the MAIC 3 results is still limited by the size of the patient populations in the intervention and comparator arms.

Table 3 Company MAIC overall survival results (adjusted)

Treatment	N	Patients with events, n (%)	Median OS (months)	Treatment effect		
				HR	95% CI	Two-sided p-value
MAIC 2						
Osimertinib	92	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo+PDC	53	[redacted]	14.1			
MAIC 3						
Osimertinib	92	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo+PDC	53	[redacted]	14.1			

CI=confidence interval; n=number; HR=hazard ratio; N=number; MAIC=matching-adjusted indirect comparison; OS=overall survival; PDC=platinum doublet chemotherapy
Source: Company response to TA416 ACD (Table 1)[9] and CDF Review CS (Appendix 7, Table 4)[3]

The AURA3 trial included a comparator PDC arm. Patients included in this arm were treated with intravenous pemetrexed (500mg/m^2 of body surface area) plus either carboplatin (target area under the curve 5 [AUC5]) or cisplatin (75mg/m^2) every 3 weeks for up to six cycles. Patients without disease progression after four cycles of platinum therapy plus pemetrexed could continue maintenance pemetrexed according to the approved label. Clinical advice to the ERG is that this treatment reflects standard of care in the NHS.

3.3 Generalisability

Box 3 NICE Appraisal Committee's preferred assumption: generalisability

The NICE AC concluded that the AURAext and AURA2 trials were broadly generalisable to clinical practice.

Source: NICE 2018[4]

Clinical advice to the ERG is that results from the AURA trials are broadly generalisable to NHS clinical practice. However, the ERG considers that the generalisability of evidence from the three AURA trials to clinical practice is unclear because of differences between trial and Systemic Anti-Cancer Therapy (SACT) dataset survival results, the latter being considerably lower than might be expected. Key information about the the three AURA trials is included in the remainder of this section and details relating to the SACT data are provided in Section 3.4.1.

3.3.1 The three AURA trials

The AURAext and AURA2 trials are both single-arm trials that provide evidence for the effectiveness of osimertinib as a treatment following failure on an EGFR-TKI. Data from these two trials were used to inform TA416[6] and critiques of these two trials were included in the ERG report (dated April 2016)[11] for that appraisal. In April 2016, the ERG concluded that the AURAext and AURA2 trials were designed and conducted to a good standard, but highlighted that data from single-arm studies are difficult to interpret due to the lack of a comparator arm and may be subject to unplanned (and unrecognised) bias and confounding.[11]

Data from the AURA3 trial were not available to inform TA416[6]; however, the company has been able to provide mature data from this trial to inform this CDF review. Unlike a Single Technology Appriaisal (STA), the CDF review process does not include a full critique of new trials. However, the ERG considers that the information about the trial that has been provided by the company gives no cause to consider that the AURA3 trial has not been designed and conducted to a good standard.

The baseline characteristics of patients recruited to the AURA3 trial are very similar to those of patients participating in the AURAext and AURA2 trials (see

Table 2). Key results are also very similar (see Table 4). These similarities, combined with similar adverse event (AE) incidence data (Company CDF Review clarification response[7] and TA416 CS[6]

Table 5 and

Table 6) suggest that results from the AURA trials are robust. The ERG highlights that the incidences of AURA3 trial AEs tend to be slightly lower than pooled AURAext/2 dataset incidence rates, perhaps reflecting the fact that patients participating in the AURA3 trial were less heavily pre-treated than most patients participating in the AURAext and AURA2 trials.

Table 4 Key results from the three AURA trials and the IMPRESS trial (MAIC 3 population)

Outcome		Trial				
		Pooled AURAext/2		IMPRESS	AURA3	
Indication		≥Second-line	Second-line	Second-line	Second-line	Second-line
Treatment		Osimertinib	Osimertinib	Placebo+ PDC	Osimertinib	PDC
Number of patients		411	92	53	279	140
ORR	Patients with responses n (%)	262/397 (66.1)	[redacted]	-	[redacted]	[redacted]
PFS	Total events n (%)	280 (68.1)	64 (69.6)	-	140 (50.2)	110 (78.6)
	Median months (95% CI)	9.9 (9.5 to 12.3)	9.7 (Not provided)	5.3	10.1 (8.3 to 12.3)	4.4 (4.2 to 5.3)
OS	Total events n (%)	271 (65.9)	[redacted]	[redacted]	188 (67.4)	93 (66.4)
	Median months (95% CI)	26.3 (24.0 to 29.1)	[redacted]	[redacted]	26.81 (23.5 to 31.5)	22.47 (20.2 to 28.8)

CDF=Cancer Drugs Fund; CS=company submission; ORR=overall response rate; OS=overall survival; PDC=platinum doublet chemotherapy; PFS=progression-free survival
Sources: Company CDF Review clarification response[7] and TA416 CS[6]

Table 5 Adverse event data from the three AURA trials (safety analysis set)

AE category	Pooled AURAext/2	AURA3	
	Osimertinib	Osimertinib	PDC
	Number (%) of patients[a]		
Sample size	411	279	136
Patients with any AE	[redacted]	[redacted]	[redacted]
CTCAE ≥Grade 3 AEs	[redacted]	[redacted]	[redacted]
SAEs	[redacted]	[redacted]	[redacted]
AE with outcome of death	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]
AEs leading to dose modification	[redacted]	[redacted]	[redacted]

[a]Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
Includes adverse events with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication.
AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events version 4.0; MedDRA version 17.1; SAE=serious adverse event
Source: CDF Review CS

Table 6 Adverse events occurring in ≥10% of AURA3 trial patients who received osimertinib

Trial	**Pooled AURAext/2***		**AURA3****			
CTCAE grade AE	**Any grade n (%)**	**Grade≥3 n (%)**	**Any grade n (%)**	**Grade≥3 n (%)**	**Any grade n (%)**	**Grade≥3 n (%)**
Treatment	Osimertinib		Osimertinib		PDC	
Indication	≥Second-line		Second-line		Second-line	
Number of patients	411		279		136	
Diarrhoea	[redacted]	[redacted]	123 (44)	3 (1)	15 (11)	2 (1)
Rash	[redacted]	[redacted]	94 (34)	2 (1)	8 (6)	0 (0)
Dry skin	[redacted]	[redacted]	65 (23)	0 (0)	4 (6)	0 (0)
Paronychia	[redacted]	[redacted]	61 (22)	0 (0)	2 (1)	0 (0)
Decreased appetite	[redacted]	[redacted]	50 (18)	3 (1)	49 (36)	4 (3)
Cough	[redacted]	[redacted]	60 (21)	0 (0)	19 (14)	0 (0)
Nausea	[redacted]	[redacted]	45 (16)	2 (1)	67 (49)	5 (4)
Fatigue	[redacted]	[redacted]	44 (16)	3 (1)	38 (28)	1 (1)
Stomatitis	[redacted]	[redacted]	41 (15)	0 (0)	21 (15)	2 (1)
Constipation	[redacted]	[redacted]	39 (14)	0 (0)	47 (35)	0 (0)
Pruritus	[redacted]	[redacted]	35 (13)	0 (0)	6 (4)	0 (0)
Vomiting	[redacted]	[redacted]	31 (11)	1 (<1)	27 (20)	3 (2)
Back pain	[redacted]	[redacted]	29 (10)	1 (<1)	12 (9)	1 (1)
Thrombocytopenia	[redacted]	[redacted]	28 (10)	1 (<1)	27 (20)	10 (7)
Nasopharyngitis	[redacted]	[redacted]	28 (10)	0 (0)	7 (5)	0 (0)
Headache	[redacted]	[redacted]	28 (10)	0 (0)	15 (11)	0 (0)
Dyspnea	[redacted]	[redacted]	24 (9)	3 (1)	18 (13)	0 (0)
Neutropenia	[redacted]	[redacted]	22 (8)	4 (1)	31 (23)	16 (12)
Leukopenia	[redacted]	[redacted]	22 (8)	0 (0)	20 (15)	5 (4)
Anaemia	[redacted]	[redacted]	21 (8)	2 (1)	41 (30)	16 (12)
Asthenia	[redacted]	[redacted]	20 (7)	3 (1)	20 (15)	6 (4)
Pyrexia	[redacted]	[redacted]	18 (6)	0 (0)	14 (10)	0 (0)
Alanine aminotransferase elevation	[redacted]	[redacted]	18 (6)	3 (1)	15 (11)	1 (1)
Aspartate aminotransferase elevation	[redacted]	[redacted]	14 (5)	3 (1)	15 (11)	1 (1)
Malaise	[redacted]	[redacted]	11 (4)	0 (0)	14 (10)	0 (0)

*AE values published in Mok 201 [13] have been presented as they are not confidential. However, the ERG notes that that there are some discrepencies between these values and those presented in Appendix2 AURA3 CSR_AiC.pdf

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events version 4.0; N=number; PDC=platinum doublet chemotherapy

Source: *CDF Review CS (Appendix 1, Table 3.2.6) and **Mok 2017[13]

3.4 Overall survival

Box 4 NICE Appraisal Committee's preferred assumption: overall survival

- *Pooling the results for the two AURA trials was reasonable given that the studies were very similar regarding baseline characteristics*
- *The available data were too immature to robustly estimate the overall survival advantage of osimertinib compared with platinum doublet chemotherapy*

Source: NICE 2018[4]

More mature data are now available from the AURAext, AURA2 and AURA3 trials (OS results calculated after approximately two-thirds of events [deaths] had occurred). Median OS results calculated from the pooled AURAext/AURA2 trial data and AURA3 trial data are of similar magnitude (see **Error! Reference source not found.**). Results from the AURA3 trial show that, for the comparison of treatment with osimertinib versus PDC, OS is not statistically significantly different.

Patients randomised to the PDC arm of the AURA3 trial were permitted to switch treatments after disease progression and 99 patients (71%) received osimertinib in this way (i.e., crossed over). As treatment with osimertinib is not currently recommended by NICE (or available via the CDF) for use as a >second-line therapy, use of osimertinib in the third-line setting does not reflect current NHS practice. The company used statistical methods to remove the effect of crossover on OS estimates for patients randomised to receive PDC.

The company considered the strengths and weaknesses of three crossover adjustment methods (the Rank Preserving Structural Failure Time Method [RPSFTM], the Inverse Probability of Censoring Weighting [IPCW] method and the two-stage method). The company considers that the RPSFTM was the most appropriate method as the IPCW and two-stage methods may produce unreliable results due to the high proportion of patients in the PDC arm who crossed over to receive osimertinib. However, the RPSFTM relies on the assumption that the treatment effect received by switchers is the same as the treatment effect received by patients initially randomised to the experimental group. This "common treatment effect" assumption may not be valid when patients only switch after disease progression, as in the AURA3 trial. Therefore, the ERG considers that the RPSFTM may not provide a valid 'uncrossed' estimate. However, all crossover adjustment methods are subject to limitations and the ERG is not aware of a crossover adjustment method that would produce valid estimates of treatment effectiveness when a high proportion of patients cross over at disease progression.

Having identified the RPFSTM as the most appropriate approach, the company then generated RPSFTM adjusted OS results using six different approaches. The approaches differed depending on the combination of assumptions about duration of treatment effect and method of censoring. The two different treatment effects considered were "on treatment" (osimertinib treatment effect assumed to only occur whilst on treatment) and "treatment group" (osimertinib treatment effect assumed to last until death/censoring). The three different re-censoring approaches were full recensoring (re-censoring applied in the estimation of the acceleration factor [AF] and the hazard ratio), recensoring applied in the estimation of the AF only, and no recensoring. In the company base case it was assumed that a treatment effect only occurred whilst on treatment and re-censoring was applied in the estimation of the AF only. Results from all analyses are provided in the CDF Review CS (Table 10). An examination of these results showed that Cox model hazard ratios ranged from [redacted] using the on treatment and full re-censoring approach, to [redacted] using the treatment group and no re-censoring approach. The [redacted]. In addition, whether one of the RPFSTM crossover adjustments carried out by the company provides more realistic results than the others is not known.

The company's crossover adjusted OS estimates for patients receiving PDC ranged from [redacted]), whilst median OS for patients from the IMPRESS trial who were matched (via MAIC) with patients in the AURAext and AURA2 trials was 14.1 months (CDF Review CS, Appendix 7, Table 4).

3.4.1 SACT data

The company has presented OS results from analyses of data from two SACT datasets:

- Patients receiving osimertinib for the treatment of metastatic EGFRm T790M mutation-positive NSCLC via the CDF
- Patients with a confirmed diagnosis of advanced or metastatic (Stage IIIB-IV) NSCLC, who have progressed following prior therapy with an approved EGFR-TKI agent (intervention not defined).

Osimertinib

Osimertinib was made available, via the CDF, to patients with specific characteristics (CDF Review CS, Appendix 3 [PHE report]), namely patients:

- With locally advanced or metastatic NSCLC that carried an EGFR and a T790M mutation
- Whose disease progression following first-line EGFR-TKI treatment with only one TKI and without any further systemic anti-cancer treatment

- Who had not received prior chemotherapy unless any prior neoadjuvant or adjuvant chemotherapy had been completed at least 6 months prior to starting first-line EGFR treatment
- With ECOG PS 0 or 1.

Data were collected between October 2016 and January 2019 (n=357, maximum follow-up period=28 months).

Data from the CDF Review CS (Appendix 3, Public Health England report) show that patients who received osimertinib via the CDF were on treatment for a median of 9 months (95% CI: 8.3 to 10.1). Median OS for these patients was 13.9 months (95% CI: 12.1 to 17.6 months). The ERG highlights that this period of time is [redacted] of that for patients participating in the three AURA trials. Reasons for this difference are not known. One possible contributing factor is that the NHS patients were older than those participating in the AURA trials (71.4% aged ≥60 years) and, therefore, are unlikely to have received further lines of treatment.

PDC

The SACT dataset related to patients (n=215) with the following characteristics:

- a recorded diagnosis of Stage IIIB or IV NSCLC in 2014 or 2015
- had received afatinib, erlobinib or gefitinib as their first chemotherapy regimen
- PS 0 or 1
- ≥28 days follow up.

The company provided OS results for two cohorts of patients (i) those who had (n=68/215) and (ii) those who had not (n=147/215) received a subsequent treatment.

The company assumed that the EGFR mutation status of patients' tumours was positive since they were prescribed an EGFR-TKI as a first-line treatment. However, the T790M status of patients' tumours on progression is not known. T790M status is important as results from a meta-analysis (three studies, 192 patients)[14] comparing survival of patients, with and without the T790M mutation, whose disease had progressed following treatment with an EGFR-TKI, showed that patients whose tumour tested positive for the T790M mutation may have had better OS and PFS outcomes compared with T790M naive patients. The pooled hazard ratios for OS and PFS were 0.66 (95% CI: 0.49 to 0.89, p=0.007) and 0.53 (95% CI: 0.35 to 0.79, p=0.002) respectively.

Median OS, calculated from SACT data collected from NHS patients who had received initial treatment with an EGFR-TKI and who, in the second-line setting received any subsequent anti-cancer treatment, was 8.31 months (95% CI: 7.92 to 11.17, n=68). The ERG highlights

that median OS for this group of patients is [redacted] of that of patients participating in the PDC arm of the AURA3 trial. Reasons for this difference are not known.

Median OS, calculated from SACT data collected from NHS patients (n=147) who had received initial treatment with an EGFR-TKI and did not receive any subsequent anti-cancer treatment, was 2.56 months (95% CI: 2.33 to 3.19).

Table 7 Available overall survival

Data set	Line of treatment	Treatment	Number	Median OS Months (95% CI)
AURAext/2 trial (pooled)	≥Second-line	Osimertinib	411	26.3 (24.0 to 29.1)
	Second-line	Osimertinib	129	26.5 (24.0 to 31.7)
AURAext/2 trial (pooled) (MAIC 3)	Second-line	Osimertinib	92	[redacted]
IMPRESS trial (MAIC 3)	Second-line	Placebo+PDC	53	14.1
AURA3 trial	Second-line	Osimertinib	279	26.8 (23.5 to 31.5)
	Second-line	PDC	140	Unadjusted: 22.5 (20.2 to 28.8)
	Second-line	PDC	140	Company base case crossover adjusted: [redacted]
SACT data	Second-line	Osimertinib	357	13.9 (12.1 to 17.6)
	Second-line	Not defined	68 147	Treated: 8.31 (7.92 to 11.17) Untreated: 2.56 (2.33 to 3.19)

CI=confidence interval; OS=overall survival; MAIC=matching-adjusted indirect comparison; PDC=platinum doublet chemotherapy; SACT=systemic anti-cancer therapy
Source: CDF Review CS (Table 6 and Appendix 7 [Table 4])

3.5 Conclusions of the clinical effectiveness section

- The AURA3 trial provides evidence of the effectiveness of osimertinib versus PDC for patients who have only previously been treated with an EGFR-TKI
- Survival results from the AURA3 trial support results from the pooled AURAext/2 dataset
- Incidences of AURA3 trial AEs tend to be slightly lower than pooled AURAext/2 dataset incidence rates, perhaps reflecting the fact that patients participating in the AURA3 trial were less heavily pre-treated than most patients participating in the AURAext and AURA2 trials
- Nearly three-quarters (71%) of patients in the PDC arm of the AURA3 trial crossed over to receive osimertinib on progression. The company considers that the RPSFTM is the most appropriate method to use to adjust for the effect of crossover.
- The ERG considers it is not possible to choose a 'best' method of crossover adjustment.The company has presented crossover adjusted results generated by six variants of the RPFSTM. All methods generate hazard ratios with [redacted]. It is not possible to determine which of the RPFSTM methods generates the most realistic results.
- The company's PDC base case median crossover adjusted OS result was more optimistic that results from the company's adjusted indirect comparison or from the SACT data (medians: [redacted]14.1 and 8.31 months respectively). These differences cast uncertainty on the generalisability of results from the three AURA trials to NHS clinical practice.

4 THE COST EFFECTIVENESS DECISION PROBLEM

The NICE AC's preferred economic assumptions (as set out in the ToE document[4]) are presented in Table 8. Further information relating to each assumption is provided in the text following the table.

Table 8 NICE Appraisal Committee's preferred clinical assumptions

Area	Summary of the NICE AC's preferred clinical assumptions
Model structure	*The company's model structure is suitable for decision making.*
Extrapolation of overall survival	*Due to the immature data the company still had to extrapolate the overall-survival results from the clinical trials to the lifetime time horizon of the model.* *The company used a Weibull distribution for the extrapolation of both osimertinib and PDC which was not implausible.* *The committee considered using a generalised gamma distribution reasonable.* *There are several plausible overall survival extrapolation curves.* *Extrapolation of overall survival is unclear and requires further data collection.*
Utilities	*Company's base-case analysis was derived from EQ-5D-5L data collected in the AURA2 study and the modelled values were not treatment specific (that is, utility was 0.815 for progression-free disease and 0.678 for post-progression disease).* *The ERG considered the utility values from the LUME-Lung 1 study could be more reasonable (that is, 0.67 utility value for both the response and stable states and 0.64 for the progressed disease state.* *The most plausible utility values fall somewhere between those used by the company and those suggested by the ERG.*
Time to treatment discontinuation	*Time to treatment discontinuation had been included appropriately in the company's revised analysis.*
End of life	*Evidence suggested that median overall survival was in the range of 20 months for people who had not had treatment before: about 15 months for people who have been previously treated with an EGFR TKI and have the T790M mutation. The short life expectancy criterion was met.* *The committee considered that because of the immaturity of the data for osimertinib, any estimate of an overall-survival gain compared with platinum doublet chemotherapy was very uncertain.* *The committee concluded that osimertinib could plausibly meet the criteria to be considered a life-extending, end-of-life treatment. However, this should be reconsidered as more data become available.*

Source: NICE 2018[4]

4.1 Model structure

Box 5 Appraisal Committee's preferred assumption: model structure

The company's model structure is suitable for decision making.

Source: NICE 2018[4]

Two models are included in the CDF Review CS (Model A and Model B). The overall structure (i.e., the way patients move between health states) of Models A and B is the same, and replicates the structure of the model submitted as part of the TA416[6] CS. Model A differs from that submitted as part of the TA416 CS only in that it includes estimates of OS, PFS and TTD from the most up to date pooled AURAext/2 data. However, there are a number of differences between Model A and Model B (see Table 9). The key differences appear to be that Model A uses OS, PFS and TTD estimates from the most up to date pooled AURAext/2 dataset and Model B uses OS, PFS and TTD estimates from the most up to date AURA3 trial data. In addition, there are worksheet layout and parameter value differences between Model A and Model B. A more comprehensive summary of the differences between Model A and Model B compiled by the ERG is provided in Appendix A.

Table 9 Summary of key differences between Model A and Model B

	Model A	Model B
Model structure	Three-state partitioned survival model	
Population	Patients with locally advanced or metastatic EGFR-T790M mutation-positive NSCLC who have progressed on or after EGFR-TKI therapy, i.e., the model is relevant to patients requiring second-line or further-line treatment	Patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR-TKI therapy, i.e., the model is relevant to patients requiring second-line
Intervention and comparators	The intervention is osimertinib and the comparator is PDC (pemetrexed+cisplatin)	
Perspective, time horizon and discounting	Perspective is that of the NHS, time horizon is set to a maximum of 15 years and cost and benefits have been discounted at a rate of 3.5%	
Modelling OS	A Weibull distribution, fitted to the latest data cut of the AURA pooled osimertinib K-M data, was used to generate OS estimates for patients receiving osimertinib. The modelling of OS for patients receiving PDC is unchanged. A Weibull distribution, fitted to data from the IMPRESS study, was used.	A log-logistic distribution, fitted to AURA3 trial osimertinib K-M data, was used to generate OS estimates for patients receiving osimertinib. This distribution was adjusted by a multiplication factor to generate OS estimates for patients receiving PDC
Modelling PFS	The company used Gompertz distributions, fitted to pooled AURAext/2 trial K-M data, and MAIC IMPRESS trial data, to generate PFS estimates for patients treated with osimertinib and PDC respectively.	A Weibull distribution, fitted to AURA3 trial osimertinib K-M data, was used to generate PFS estimates for patients receiving osimertinib. This distribution was adjusted by a multiplication factor to generate PFS estimates for patients receiving PDC.
Modelling TTD treatment	Osimertinib: AURA2 trial TTD data used directly up to 14.3 months. Estimates 14.3 months to 15 years (model time horizon) were generated using a log-logistic extrapolation. PDC: PFS estimates used up to a maximum of 4 cycles of treatment.	Osimertinib: Generalised gamma distributions were used to estimate TTD for osimertinib and PDC separately.
HRQoL	Utility values used to generate FAD ICERs per QALY gained: PF: 0.831 Stable disease: 0.751 PD: 0.715	Values derived from EQ-5D-5L data (crosswalked to EQ-5D-3L) collected as part of the AURA3 trial: PF: 0.836 Stable disease: 0.797 PD: 0.717
Resources and costs	Resource use and costs were estimated based on information from the AURAext/2 studies and the IMPRESS trial, published sources and advice from clinical and economic experts.	Resource use and costs were estimated based on information from the AURA3 study. Many of the resources used and the costs allocated to those resources differed from the resource use and cost assumptions agreed by the NICE AC prior to admission to the CDF.

AC=Appraisal Committee; CDF=Cancer Drugs Fund; DC=data cut; FAD= final appraisal determination; ICER=incremental cost effectiveness ratio; K-M=Kaplan-Meier; NSCLC=non-small cell lung cancer; PDC=platinum doublet chemotherapy; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation

Using Model A, the ERG has been able to replicate the ICERs per QALY gained reported by the company in Table 17 (p33) of the CDF Review CS (cost effectiveness analyses 1-3a). Using Model B, the ERG has been able to replicate the ICERs per QALY gained reported by the company in Table 17 (p33) of the CDF Review CS (cost effectiveness analyses 4 and 4a).

The ERG considers that the direct clinical effectiveness data from the AURA3 trial (osimertinib versus PDC) form a more appropriate basis for decision making than the pooled AURAext/2 data. Both sets of data are mature and OS, PFS and TTD results are similar. The AURA3 trial has the advantage of including a relevant comparator arm. Following discussion with the NICE technical team, the ERG has created a hybrid model (Model A/B) which meets the ToE for this review[4] better than either Model A or Model B. Model A/B has been constructed by replacing the OS, PFS and TTD data in Model A with OS, PFS, TTD data from the AURA3 trial (Model B). Instructions for the creation of Model A/B are provided in Appendix B.

4.2 Overall survival

Box 6 NICE Appraisal Committee's preferred assumption: overall survival

Due to the immature data the company still had to extrapolate the overall-survival results from the clinical trials to the lifetime time horizon of the model.

The company used a Weibull distribution for the extrapolation of both osimertinib and PDC which was not implausible.

The committee considered using a generalised gamma distribution a potentially more reasonable.

There are several plausible overall survival extrapolation curves.

Extrapolation of overall survival is unclear and requires further data collection.

Source: NICE 2018[4]

The company submitted updated pooled AURAext/2 clinical effectiveness data (Model A) and the most recent data from the AURA3 trial (Model B).

The company assessed the proportionality of AURA3 trial (osimertinib versus PDC) OS hazards (see CDF Review CS, Appendix 9 for details) and concluded that there was no evidence of non-proportionality. Results from ERG analyses support the company's conclusion. The company used this conclusion to support their approach to modelling OS; they fitted a parametric curve to the AURA3 trial, crossover-adjusted, osimertinib OS K-M data and used a multiplication factor to adjust these K-M data to represent the OS of patients treated with PDC.

The company assessed the fit of six parametric distributions to the AURA3 osimertinib OS K-M data. The company concluded that none of these parametric distributions fitted the

underlying data, particularly "…the flat tail given from the observed data from ~37 months" (CDF Review CS, Appendix 9, p11). The company stated that they chose the log-logistic distribution as it provided the closest estimate to the tail of the data, and generated the most optimistic OS estimates in the longer-term. In contrast, in Model A, Weibull distributions were fitted to the osimertinib and PDC datasets.

4.3 Time to treatment discontinuation

Box 7 NICE Appraisal Committee's preferred assumption: time to treatment discontinuation

Time to treatment discontinuation had been included appropriately in the company's revised analysis.

Source: NICE 2018[4]

In Model A, for PDC, the company used their modelling of PFS based on MAIC IMPRESS trial data to estimate TTD. In Model A, for osimertinib, the company used AURA2 TTD data for 14 months and then estimated TTD with a log-logistic distribution.

The AURA3 PDC TTD estimates are almost complete and so do not require extrapolation. The AURA3 osimertinib TTD data are available up to a maximum of 52 months. In Model B, the company used generalised gamma distributions to model TTD for osimertinib and PDC.

4.4 Utilities

Box 8 NICE Appraisal Committee's preferred assumption: utilities

Company's base-case analysis were derived from EQ-5D-5L data collected in the AURA2 study and the modelled values were not treatment specific (that is, utility was 0.815 for progression-free disease and 0.678 for post-progression disease).

The ERG considered the utility values from the LUME-Lung 1 study could be more reasonable (that is, 0.67 utility value for both the response and stable states and 0.64 for the progressed disease state.

The most plausible utility values fall somewhere between those used by the company and those suggested by the ERG. The ERG considered the utility values from the LUME-Lung 1 study could be more reasonable (that is, 0.67 utility value for both the response and stable states and 0.64 for the progressed disease state.

The most plausible utility values fall somewhere between those used by the company and those suggested by the ERG.

Source: NICE 2018[4]

The company used the same utility values in Model A as were included in the TA416[6] model; the ERG used these values in Model A/B.

The utility values used in Model B were derived from EQ-5D-5L data (cross-walked to EQ-5D-3L) collected during the AURA3 trial. The values used were 0.836 for the progression-free

disease health state, 0.797 for the stable disease health state and 0.717 for the post-progression disease health state.

4.5 End of Life

Box 9 NICE Appraisal Committee's preferred assumption: end of life

Evidence suggested that median overall survival was in the range of 20 months for people who had not had treatment before: about 15 months for people who have been previously treated with an EGFR TKI and have the T790M mutation. The short life expectancy criterion was met.

The committee considered that because of the immaturity of the data for osimertinib, any estimate of an overall-survival gain compared with platinum doublet chemotherapy was very uncertain.

The committee concluded that osimertinib could plausibly meet the criteria to be considered a life-extending, end-of-life treatment. However, this should be reconsidered as more data become available.

Source: NICE 2018[4]

For the comparison of treatment with osimertinib versus PDC, the ERG discusses the NICE End of Life[15] criteria in Section 5.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company has presented results from a number of deterministic cost effectiveness analyses (see CDF Review CS, Table 17). Different combinations of study data, survival extrapolations and utility values have been used to generate cost effectiveness results. The cost effectiveness estimates from each of the company's analyses are shown in Table 10. None of these analyses generated an ICER per QALY gained below £50,000 per QALY gained.

Table 10 Company's cost effectiveness estimates

	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Cost effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost effectiveness at CDF entry (TA416)							
Osimertinib	£81,631	3.05	1.98	£58,472	1.22	0.83	£70,776
PDC	£23,159	1.82	1.15	-	-	-	-
Model A							
Cost effectiveness analysis 2: Analysis that demonstrated plausible potential for cost effectiveness at CDF entry – incorporating updated clinical evidence (company preferred utilities)							
Osimertinib	£79,846	2.84	2.12	£56,687	1.02	0.82	£69,453
PDC	£23,159	1.83	1.30	-	-	-	-
Cost effectiveness analysis 3: New company base case, using company preferred utilities							
Osimertinib	£80,034	2.87	2.14	£56,875	1.05	0.84	£68,015
PDC	£23,159	1.83	1.30	-	-	-	-
Cost effectiveness analysis 3a: New company base case, sensitivity analysis, using ERG preferred utilities							
Osimertinib	£80,034	2.87	1.86	£56,875	1.05	0.71	£79,895
PDC	£23,159	1.83	1.15	-	-	-	-
Model B							
Cost effectiveness analysis 4: AURA 3 analysis, using company preferred utilities							
Osimertinib	£107,546	3.08	2.30	£73,155	1.03	0.82	£88,877
PDC	£34,278	2.05	1.48	-	-	-	-
Cost effectiveness analysis 4a: AURA 3 analysis, using ERG preferred utilities							
Osimertinib	£107,546	3.08	1.99	£73,155	1.03	0.70	£104,536
PDC	£34,278	2.05	1.29	-	-	-	-

CDF=Cancer Drug Fund; ICER=incremental cost-effectiveness ratio; LYG=life years gained; PDC=platinum doublet chemotherapy; QALYs=quality adjusted life year
Source: CDF Review CS, Table 17 p.33

6 EVIDENCE REVIEW GROUP ADDITIONAL ANALYSES

6.1 Model A/B base case

The ERG considers the AURA3 trial to be the most appropriate data source from which to estimate the comparative OS of osimertinib versus PDC and that the PFS and TTD data from the AURA3 trial should so be used to inform this CDF Review. The ERG considers neither Model A nor Model B are in line with the terms set out in the ToE for this review.[4] With agreement from the NICE technical team, the ERG has created a hybrid model (Model A/B) which meets the ToE for this review[4] better than either Model A or Model B.

Model A/B has been constructed by inserting AURA3 trial OS, PFS and TTD data (used in Model B) into Model A. In the company models, a mid-cycle correction was applied to TTD data; this approach means that, in the first model cycle, not all patients receive their allocated treatment and this leads to an underestimate of the cost of treatment. This minor error was corrected before generating Model A/B cost effectiveness results. All other parameters in Model A/B remain unchanged from the model used at CDF entry (Model A).

The cost effectiveness results generated by Model A/B are presented in

Table **11**. The mean estimates of survival generated by Model A/B are shown in Table 12.

Table 11 Cost effectiveness analysis (Model A/B)

Treatment	Total cost	Total LYG	Total QALYs	Incremental			ICER per QALY gained
				Cost	LYG	QALYs	
Osimertinib*	£92,560	3.082	2.284				
PDC	£23,769	2.052	1.468	£68,792	1.030	0.817	£84,209

ICER=incremental cost effectiveness ratio; LYG=life year gained; PAS=patient access scheme; QALY=quality adjusted life year
* Confidential discounted prices used to estimate the cost of treatment

Table 12 Mean PFS, TTD and OS in Model A/B

Treatment	PFS months (mean)	TTD months (mean)	OS months (mean)
Osimertinib	11.531	[redacted]	36.980
PDC	5.704	[redacted]	24.624

PDC=platinum doublet chemotherapy; PFS=progression-free survival; OS=overall survival; TTD=time to treatment continuation

6.2 Exploratory and sensitivity analyses undertaken by the ERG

6.2.1 Utility values

The utility estimates generated from data collected during the AURA3 trial are very similar to those generated from data collected during the AURA2 trial. The ERG TA416 report[11] includes alternative cost effectiveness results generated using utility values from the LUME-Lung 1 trial[1] (pre-progression=0.67, post-progression=0.64). The NICE AC concluded that the true utility values associated with the pre-progression and post-progression health states are likely to lie somewhere between the estimates from the AURA2 trial and the LUME-Lung 1 trial.[1] The ERG has, therefore, also generated cost effectiveness results using LUME-Lung 1 trial[1] utility values in Model A/B.

Compared with Model A/B base case, this leads to a (0.17) decrease in incremental QALYs (from 0.82 to 0.65) and no change to incremental costs, increasing the ICER per QALY gained for the comparison of osimertinib versus PDC from £84,209 to £105,693.

6.2.2 Survival and treatment costs

For OS, PFS and TTD the company has estimated parametric curves based upon AURA3 trial data. The ERG preferred approach is to use K-M data from trials directly followed by extrapolation of the K-M data after the point at which the K-M data become heavily censored and unreliable. In choosing distributions for extrapolation, cumulative hazard plots of AURA3 trial K-M data for OS, PFS and TTD for osimertinib and PDC were built (cumulative hazard plots are provided in Appendix C). In each case, a constant hazard trend (i.e., a straight line) became evident before the end of the K-M data and so it was appropriate to extrapolate the available K-M data in all cases using exponential functions.

The ERG therefore remodelled OS, PFS and TTD data for osimertinib and PDC using exponential functions. Compared with the company Model A/B base case, this approach reduces the ICER per QALY gained by £10,644.

7 IMPACT ON COST EFFECTIVENESS OF ERG ADDITIONAL ANALYSES

A summary of the impact of the ERG's amendments to Model A/B on the cost effectiveness of osimertinib versus PDC for the treatment of patients with advanced or metastatic EGFR T790M mutation-positive disease in the second-line setting after failure of an EGFR-TKI is provided in Table 13.

Using the CAA[2] price for treatment with osimertinib and list prices for pemetrexed and cisplatin, the ERG has made four amendments to Model A/B as detailed in Section 3.2. The ERG presents the results of each amendment individually in Table 13. The ERG also presents the results of two scenarios:

- Scenario 1: changes to OS, PFS and TTD
- Scenario 2: changes to OS, PFS, TTD and using LUME-Lung 1 trial[1] utility values.

Details of all Microsoft Excel revisions carried out by the ERG to Model A/B are presented in Appendix D of this ERG report.

7.1 Conclusions of the cost effectiveness section

The company's submitted ICERs per QALY gained (CDF Review CS, Table 17) ranged from £68,015 to £104,536.

The ERG's hybrid Model A/B yields a base case ICER per QALY gained of £84,209. Compared with PDC, Model A/B base case cost effectiveness results show that treatment with osimertinib generates more QALYs but at an additional cost.

Using Model A/B as the base case, the ERG's revised ICERs per QALY gained range between £73,565 and £105,693. When all of the ERG amendments are combined, the ICER per QALY gained is £91,812.

Table 13 ERG adjustments to Model A/B base case: osimertinib (Commercial Access Agreement price) versus PDC (list prices)

ERG amendment/scenario	Osimertinib			PDC			Incremental			*ICER*	
	Cost	Life years	QALYs	Cost	Life years	QALYs	Cost	Life years	QALYs	£/QALY	Change from base case
A. Model A/B base case	£92,560	3.082	2.284	£23,769	2.052	1.468	£68,792	1.030	0.817	£84,209	
R1) ERG modelling of OS	£91,003	2.808	2.089	£21,348	1.702	1.217	£69,655	1.106	0.871	£79,942	-£4,267
R2) ERG modelling of PFS	£91,130	3.082	2.311	£23,761	2.052	1.468	£67,369	1.030	0.843	£79,925	-£4,284
R3) ERG modelling of TTD	£90,321	3.082	2.284	£24,027	2.052	1.468	£66,295	1.030	0.817	£81,153	-£3,057
R4) LUME-Lung 1 utility values	£92,560	3.082	1.996	£23,769	2.052	1.345	£68,792	1.030	0.651	£105,693	£21,484
Scenario 1: R1)+R2)+R3)	£87,585	2.808	2.115	£21,575	1.702	1.218	£66,011	1.106	0.897	£73,565	-£10,644
Scenario 2: R1)+R2)+R3)+R4)	£87,585	2.808	1.830	£21,575	1.702	1.111	£66,011	1.106	0.719	£91,812	£7,602

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years; TTD=time to treatment discontinuation

8 END OF LIFE

The NICE End of Life criteria[15] are:

- treatment is indicated for patients with a short life expectancy, normally less than 24 months and
- there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

Short life expectancy

The company's AURA3 crossover adjusted median OS estimates for patients receiving PDC ranged from [redacted] months to [redacted] months. The company's mean estimate of OS for patients receiving PDC from their modelling of OS from AURA3 trial data is 24.6 months. The ERG's revised estimate of OS for patients receiving PDC produces a mean estimate of 20.4 months. The ERG therefore considers that the short life expectancy criterion is met.

Life extension

A comparison of the company's AURA3 trial crossover adjusted median OS results show the difference between treatment with osimertinib and PDC to be a minimum of [redacted] months ([redacted] months versus [redacted] months respectively) and a maximum of [redacted] months ([redacted] months versus [redacted] months respectively).

From the company's modelling of AURA3 data, mean estimates of OS are 36.9 months for osimertinib and 24.6 months for PDC.

The ERG's revised mean estimates of OS are 33.7 months for osimertinib and 20.4 months for PDC. The ERG therefore considers that the life extension criterion is met.

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10 APPENDICES

10.1 Appendix A: Main differences between Model A and Model B

	Model A		***Model B***	
Sheet	**Parameter**	**Value**	**Parameter**	**Value**
T790_test	ctDNA	£472	ctDNA	£472.11
	Patients needed to test	1.66	Patients needed to test	1.87
	Tissue biopsy tests performed	0.60	Tissue biopsy tests performed	0.83
	ctDNA tests performed	0.80	ctDNA tests performed	0.17
	Tissue biopsy number of tests per patient per treatment - osimertinib	1	Tissue biopsy number of tests per patient per treatment - osimertinib	1.55
	ctDNA tests number of tests per patient per treatment - osimertinib	1.33	ctDNA tests number of tests per patient per treatment - osimertinib	0.32
	Total cost of testing per patient	£1350.80	Total cost of testing per patient	£1277.30
Differences in the assumptions in the number of tests leads to a decrease in total testing costs in Model B				
Response_B	Overall response rate	67.4%	Overall response rate	70.6%
	Relative response rate versus reference treatment - osimertinib	1.00	Relative response rate versus reference treatment - osimertinib	1.00
	Relative response rate versus reference treatment - PDC	0.49	Relative response rate versus reference treatment - PDC	0.44
Response rates from AURA2 in Model A and AURA3 in Model B				
Osimertinib				
Safety_data	AEs	Number of events	AEs	Number of events
	Anaemia	2	Abdominal pain	0
	Decreased appetite	1	Anaemia	3
	Diarrhoea	2	Asthenia	2
	Dyspnoea	2	Decreased appetite	5
	Nausea	1	Epilepsy	0
	Platelet count decreased	1	Hyperglycaemia	1
	Vomiting	2	Hypokalaemia	0
			Hyponatraemia	5
			Nausea	3
			Neutropenia	2
			Neutrophil count decrease	4
			Platelet count decreased	2
			Pulmonary embolism	8
			Thrombocytopenia	1
			Vomiting	3

			White blood cell count decrease	1
PDC				
Safety_data	Anaemia	5	Abdominal pain	3
	Decreased appetite	3	Anaemia	15
	Diarrhoea	1	Asthenia	6
	Dyspnoea	3	Decreased appetite	4
	Fatigue / Asthenia	4	Epilepsy	3
	Headache	1	Hyperglycaemia	3
	Hyperglycemia	1	Hypokalaemia	3
	Nausea	6	Hyponatraemia	3
	Neutropenia	20	Nausea	5
	Stomatitis	1	Neutropenia	8
	Vomiting	3	Neutrophil count decrease	10
			Platelet count decreased	5
			Pulmonary embolism	3
			Thrombocytopenia	5
			Vomiting	3
			White blood cell count decrease	3
Adverse event rates from AURA2 in Model A and AURA3 in Model B				
N.B. The order of AEs changed (alphabetised) in this table from the order in Model A to enable clearer comparison				
Progression-free resource use (weekly)				
Costs_Dis	Follow-up OP Visit	0.184	Physician visit (surgery)	0.231
	Chest X-ray	0.130	Palliative care visit	1.000
	CT scan (chest)	0.012	Radiotherapy (brain)	0.067
	CT scan (other)	0.007	Radiotherapy (bone)	0.067
	ECG	0.020	99Tc bone scintigraphy scan	0.333
	Community Nurse Visit	0.167	Chest X-ray	0.093
	GP Surgery Visit	0.230		
	Clinical Nurse Specialist Visit	0.230		
Progression-free unit costs				
Costs_Dis	Follow-up OP Visit	£138.37	Physician visit (surgery)	£68.65
	Chest X-ray	£30.00	Palliative care visit	£87.09
	CT scan (chest)	£116.00	Radiotherapy (brain)	£129.10
	CT scan (other)	£132.00	Radiotherapy (bone)	£129.10
	ECG	£175.00	99Tc bone scintigraphy scan	£237.71
	Community Nurse Visit	£67.00	Chest X-ray	£30.74
	GP Surgery Visit	£44.00		
	Clinical Nurse Specialist Visit	£91.00		
	Total progression-free costs (weekly)	£77.44	Total progression-free costs (weekly)	£202.25

Post-progression resource use (weekly)				
Costs_Dis	Follow-up OP Visit	0.152	Physician visit (home visit)	0.500
	Chest X-ray	0.125	Palliative care visit	1.000
	CT scan (chest)	0.005	Radiotherapy (per fraction)	0.167
	CT scan (other)	0.008	Blood transfusion	0.167
	ECG	0.017	Oxygen	0.167
	Community Nurse Visit	0.167	99Tc bone scintigraphy scan	0.067
	GP Surgery Visit	0.500	X-ray	0.093
	Clinical Nurse Specialist Visit	0.230		
	Therapist Visit	0.500		
Post-progression unit costs				
Costs_Dis	Follow-up OP Visit	£138.37	Physician visit (home visit)	£115.78
	Chest X-ray	£30.00	Palliative care visit	£87.09
	CT scan (chest)	£116.00	Radiotherapy (per fraction)	£129.10
	CT scan (other)	£132.00	Blood transfusion	£199.80
	ECG	£175.00	Oxygen	£14.37
	Community Nurse Visit	£67.00	99Tc bone scintigraphy scan	£237.71
	GP Surgery Visit	£112.22	X-ray	£30.74
	Clinical Nurse Specialist Visit	£91.00		
	Therapist Visit	£44.00		
	Total post-progression costs (weekly)	£139.58	Total post- progression costs (weekly)	£220.91
Terminal- care costs one-off resource use				
Costs_Dis	Hospital	0.56	Hospital	0.56
	Hospice	0.17	Hospice	0.17
	Home	0.27	Home	3.82
Terminal-care resource use				
Costs_Dis	Hospital	£3228.37	Hospital	£3728.16
	Hospice	£4035.46	Hospice	£3728.16
	Home	£5207.80	Home	£87.09
	Total terminal care costs	£3905.35	Total terminal care costs	£3042.86
Resource use items and the costs of those items differs between the models. This results in higher costs in the pre-progression and post-progression health states in Model B and lower costs in Model A for terminal care.				
Admin costs – first visit				
Costs_Tx	Not included	Not included	Osimertinib	0.00
			PDC	£269.75
Admin costs – after first visit				
Costs_Tx	Osimertinib	£0.48	Osimertinib	0.00
	PDC	£332.50	PDC	£269.75
Small difference to osimertinib admin costs. The higher cost for an initial visit is not included in Model A				
Time spent on subsequent therapy				

Costs_SubTx	Osimertinib	16.38	Osimertinib	20.39
	Platinum doublet chemo	2.43	Platinum doublet chemo	3.38
	Pemetrexed monotherapy (exc.)	2.32	Pemetrexed monotherapy (exc.)	3.36
	Docetaxel monotherapy (exc.)	2.32	Docetaxel monotherapy (exc.)	2.44
	TKI monotherapy (exc.)	2.43		
	TKI combination therapy (exc.)	2.43		
	CO-1686 (exc.)	0.00		
	BSC (exc.)	2.43		
	Chemo monotherapy (exc.)	0.00		
Fewer subsequent therapy options in Model B, with an increase in the duration of subsequent therapy for those that are the same as in Model A				
AE costs				
Costs_AE	Anaemia	£3110.11	Abdominal pain	0.00
	Back Pain	£1679.85	Anaemia	£1002.07
	Constipation	£2367.66	Asthenia	£379.11
	Cough	0	Decreased appetite	£81.97
	Decreased appetite	£2367.66	Epilepsy	0.00
	Diarrhoea	£2411.2	Hyperglycaemia	0.00
	Dyspnoea	£1447.73	Hypokalaemia	0.00
	Fatigue / Asthenia	£3110.11	Hyponatraemia	0.00
	Febrile neutropenia	£2426.86	Nausea	£1966.24
	Headache	£1344.07	Neutropenia	£354.52
	Hyperglycemia	0	Neutrophil count decrease	0.00
	Nausea	£2245.09	Platelet count decreased	0.00
	Neutropenia	£2426.86	Pulmonary embolism	0.00
	Oedema peripheral	£1759.98	Thrombocytopenia	0.00
	Platelet count decreased	£2425.65	Vomiting	£1966.24
	Pruritus	0	White blood cell count decrease	0.00
	Rash (grouped term)	£2666.09		
	Stomatitis	£1483.11		
	Upper respiratory tract infection	0		
	Vomiting	£2245.09		
The AEs listed follow those reported in AURA2 for Model A and AURA3 for Model B. There are some differences in costs for those that are common in both models.				
N.B. The order of AEs changed (alphabetised) in this table from the order in Model A to enable clearer comparison				
Health states				
Utilities	CR/PR	0.831	CR/PR	0.836
	SD	0.751	SD	0.797
	Post-progression	0.715	Post-progression	0.717
AE disutilities				
Utilities	Anaemia	0.073	Abdominal pain	0.050

	Back Pain	0.05	Anaemia	0.073
	Constipation	0.05	Asthenia	0.073
	Cough	0.05	Decreased appetite	0.000
	Decreased appetite	0.05	Epilepsy	0.050
	Diarrhoea	0.047	Hyperglycaemia	0.050
	Dyspnoea	0.05	Hypokalaemia	0.050
	Fatigue / Asthenia	0.21	Hyponatraemia	0.050
	Febrile neutropenia	0.09	Nausea	0.048
	Headache	0.05	Neutropenia	0.090
	Hyperglycemia	0	Neutrophil count decrease	0.050
	Nausea	0.048	Platelet count decrease	0.050
	Neutropenia	0.09	Pulmonary embolism	0.050
	Oedema peripheral	0.05	Thrombocytopenia	0.050
	Platelet count decreased	0.05	Vomiting	0.048
	Pruritus	0	White blood cell count decrease	0.050
	Rash (grouped term)	0.032		
	Stomatitis	0.05		
	Upper respiratory tract infection	0		
	Vomiting	0.048		
The AEs listed follow those reported in AURA2 for Model A and AURA3 for Model B. Most of those that appear in both models have the same value, however, there are some differences between those that are common in both models.				
N.B. The order of AEs changed (alphabetised) in this table from the order in Model A to enable clearer comparison				

10.2 Appendix B: Instructions for the creation of Model A/B

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
Survival curves (OS and PFS)	Model B to model A	ClinicalData_B	Model b K7:X12 To Model a CN7:DA12	Lift the survival functions for osimertinib from the live values section of model b and paste values into the live values section of model a
	Model B to model A		Model b K35:X40 To Model a CN35:DA40	Repeat for PDC
	Model A	Survival_B	K34 & K48	Switch the choice of parametric curve to log-logistic
			S34 & S48	Switch the choice of parametric curve to Weibull
TTD	Model B	ResSurv_B	HW22:HW802	AURA3 Osi company TTD – without mid-cycle correction Copy
	Model A	Create new sheet and name in AURA3_TTD	A2	Paste values
			A1	Add label “Osi”
	Model B	ResSurv_B	IA22:IA802	AURA3 PDC company TTD – without mid-cycle correction Copy
	Model A	AURA3_TTD	B2	Paste values
			B1	Add label “PDC”
	Model A	PatFlow_B	DE13 Copy down to DE792	Osi company AURA3 TTD =’AURA3_TTD’!A2
			DD13 Copy down to DD792	PDC company AURA3 TTD =’AURA3_TTD’!B2
	Model A	Cost_calc	Model a V13 Copy down to V792	Use: =(IF(TTD_TrueFalse,(INDEX(Patflow_area,$C13,S$6+96)*IF($B13>=V$9,0,V$11)),(SUM(INDEX(Patflow_area,$C13,S$6+2),INDEX(Patflow_area,$C13,S$6+3))*IF($B13>=V$9,0,V$11)))*$D13)
Save as a new model.				

10.3 Appendix C: ERG cumulative hazard plots for OS, PFS and TTD

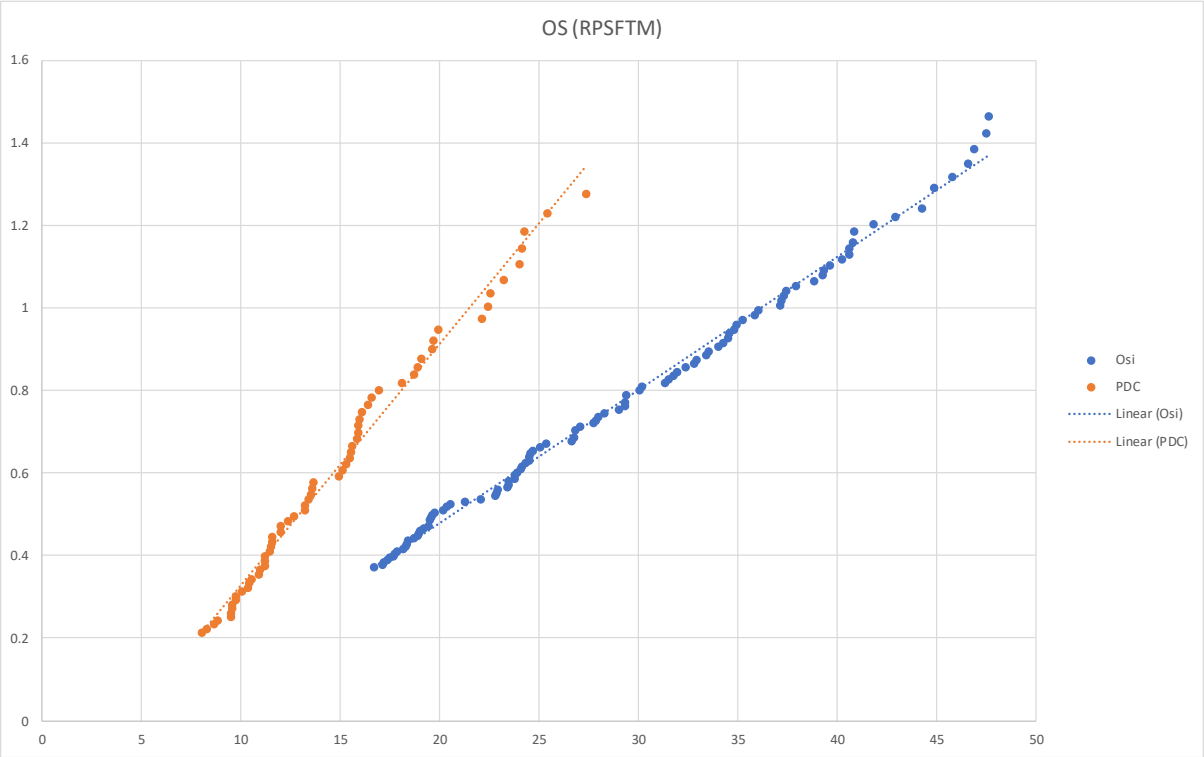


Figure 1 AURA3 OS K-M data cumulative hazard plots

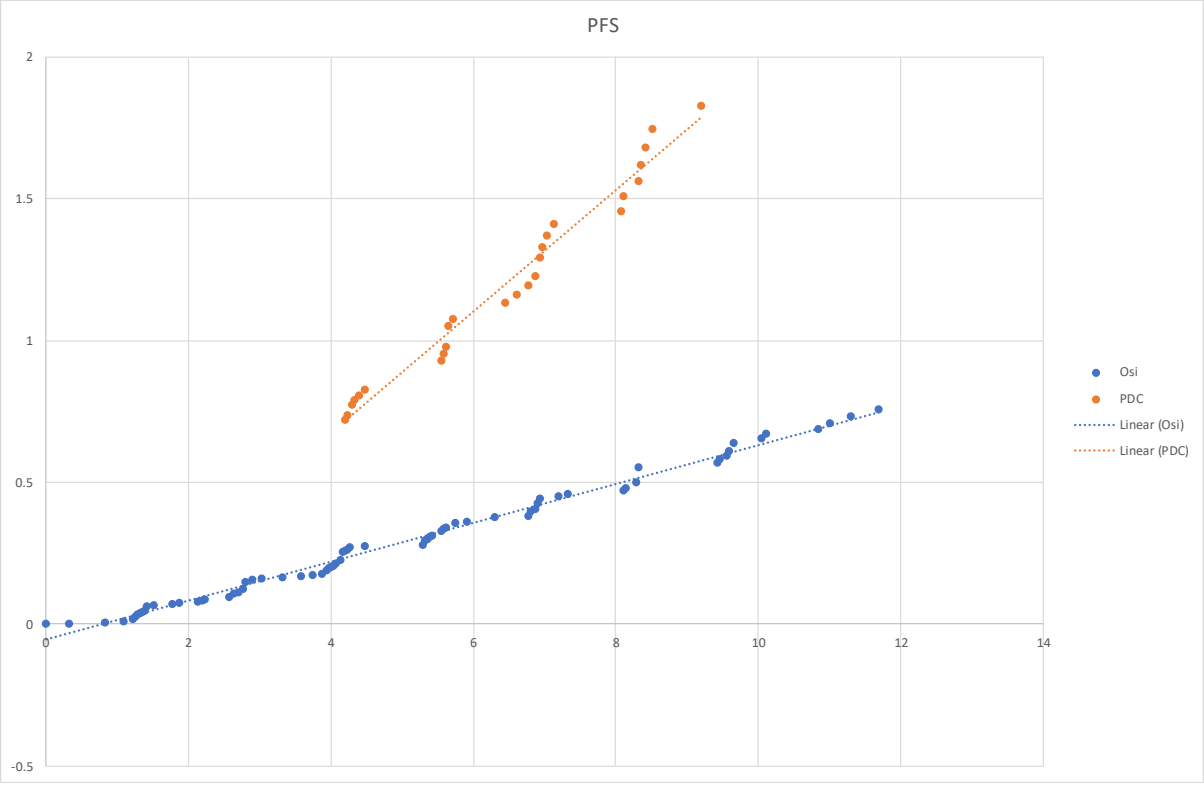


Figure 2 AURA3 PFS K-M data cumulative hazard plots

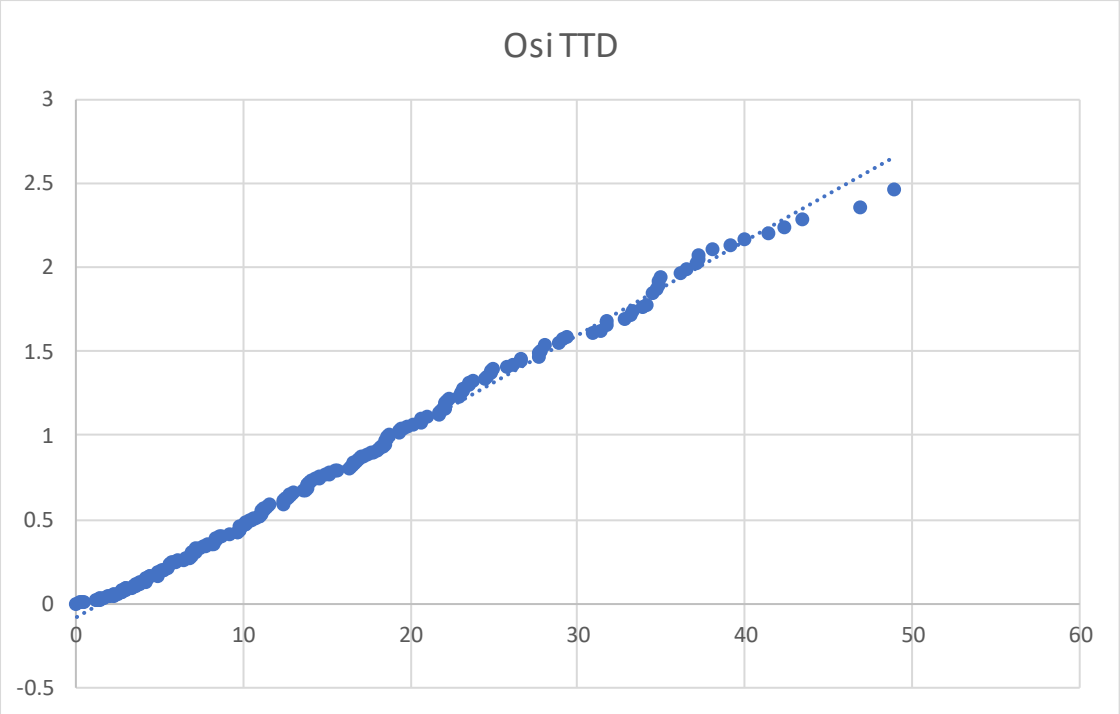


Figure 3 AURA3 TTD K-M data cumulative hazard plots

10.4 Appendix D: ERG Microsoft EXCEL revisions to Model A/B

All revisions are activated by a logic switch with:

0=unchanged

1=apply ERG modification

Logic switches are indicated by named range variables Mod_*letter* where letter = A - D.

A menu of revisions and Mod names appear below and on the 'Results' worksheet together with summary results as used to transfer to the ERG report.

Revision #	Modification name	Switch	Description
R4)	Mod_A	0	ERG suggested utility values
R2)	Mod_B	0	ERG estimates of PFS based on the AURA3 trial data
R3)	Mod_C	0	ERG estimates of TTD based on the AURA3 trial data
R1)	Mod_D	0	ERG estimates of OS based on the AURA3 trial data

Instructions for modifying the company model

1. Move all sheets from *Osi 1577_ERG additional model data (CiC).xlsx* into company model

2. Create named switches for each of the modifications mod_A to mod_D

3. For each sheet given in the 'Sheet' column below:
    - copy formulae from the 'Modified formulae' column in the table below
    - paste formulae into the cells referred to in the 'Cells' column in the table below

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R4) Use ERG suggested utility values	Mod_A	CountryData Add modification to three utility options in this sheet	G680	Use ERG suggested utility value for pre-progression =IF(mod_A=1,0.67,0.833)
			H680	Use ERG suggested utility value for pre-progression =IF(mod_A=1,0.67,0.891)
			I680	Use ERG suggested utility value for pre-progression =IF(mod_A=1,0.67,0.831)
			G681	Use ERG suggested utility value for pre-progression for stable disease also =IF(mod_A=1,0.67,0.753)
			H681	Use ERG suggested utility value for pre-progression for stable disease also =IF(mod_A=1,0.67,0.825)
			I681	Use ERG suggested utility value for pre-progression for stable disease also =IF(mod_A=1,0.67,0.751)
			G682	Use ERG suggested utility value for post-progression =IF(mod_A=1,0.64,((0.751+0.679)/2))
			H682	Use ERG suggested utility value for post-progression =IF(mod_A=1,0.64,0.821)
			I682	Use ERG suggested utility value for post-progression =IF(mod_A=1,0.64,((0.751+0.679)/2))
			G688	Use ERG suggested utility value for pre-progression =IF(Mod_A=1,0.67,0.833)
			H688	Use ERG suggested utility value for pre-progression =IF(Mod_A=1,0.67,0.891)
			I688	Use ERG suggested utility value for pre-progression =IF(Mod_A=1,0.67,0.831)
			G689	Use ERG suggested utility value for pre-progression for stable disease also =IF(Mod_A=1,0.67,0.753)
			H689	Use ERG suggested utility value for pre-progression for stable disease also =IF(Mod_A=1,0.67,0.825)
			I689	Use ERG suggested utility value for pre-progression for stable disease also =IF(Mod_A=1,0.67,0.751)
			G690	Use ERG suggested utility value for post-progression =IF(Mod_A=1,0.67,((0.751+0.679)/2))

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
			H690	Use ERG suggested utility value for post-progression =IF(Mod_A=1,0.67,0.821)
			I690	Use ERG suggested utility value for post-progression =IF(Mod_A=1,0.67,((0.751+0.679)/2))
R2) Use ERG re-modelled PFS data from AURA3	Mod_B	ResSurv_B	E22 copy down to E802	Use AURA3 ERG re-modelled PFS for osimertinib =IF(Mod_B=1,'ERG - PFS'!A4,IF(OR(analysis_nr=1,INDEX(surv_model_nr,E$13)=1,SUM(E$17:E$20)=0),0,Survival_func(E$16:E$20,$C22)))
			G22 copy down to G802	Use AURA3 ERG re-modelled PFS for PDC =IF(Mod_B=1,'ERG - PFS'!B4,IF(OR(analysis_nr=1,INDEX(surv_model_nr,G$13)=1,SUM(G$17:G$20)=0),0,Survival_func(G$16:G$20,$C22)))
R1) Use ERG re-modelled OS data from AURA3	Mod_D	ResSurv_B	F22 copy down to F802	Use AURA3 ERG re-modelled OS for osimertinib =IF(Mod_D=1,'ERG - OS'!A3,IF(OR(analysis_nr=1,INDEX(surv_model_nr,F$13)=1,SUM(F$17:F$20)=0),0,CHOOSE(surv_param_model,Survival_func(F$16:F$20,$C22),ClinicalData_B!DV22)))
			H22 copy down to H802	Use AURA3 ERG re-modelled OS for PDC =IF(Mod_D=1,'ERG - OS'!B3,IF(OR(analysis_nr=1,INDEX(surv_model_nr,H$13)=1,SUM(H$17:H$20)=0),0,CHOOSE(surv_param_model,Survival_func(H$16:H$20,$C22),ClinicalData_B!DX22)))
R3) Use ERG re-modelled TTD data from AURA3	Mod_C	PatFlow_B	NB: PDC then OS in this sheet DE13 copy down to DE792	Use AURA3 ERG re-modelled TTD for osimertinib =IF(Mod_C=1,'ERG - TTD'!A3,'AURA3_TTD'!A2)
			DD13 copy down to DD792	Use AURA3 ERG re-modelled TTD for PDC =IF(Mod_C=1,'ERG - TTD'!B3,'AURA3_TTD'!B2)

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer [ID1559]

Cancer Drugs Fund update of TA416

ERRATUM v2

This report was commissioned by the NIHR Systematic Reviews Programme as project number 129027

Completed 18 December 2019

CONTAINS **********

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

ERRATUM

The ERG identified an error in their amendments to the company model and accompanying instructions. In the LUME-Lung 1 utility values scenario, the utility value for the post-progression health state for platinum doublet chemotherapy (PDC) was set to 0.67, instead of 0.64.

The ERG has corrected this error and has included p10, p35, pp37-38, pp51-52 from the ERG report with the amendments in red text.

1.1 Summary of key issues in cost effectiveness evidence

Two models are included in the CDF Review CS (Model A and Model B). The basic structure of Models A and B and the model submitted as part of the TA416 CS were the same. Model A differed from that submitted as part of the TA416 CS only in that it included estimates of OS, PFS and TTD from the most up to date pooled AURAext/2 data. The key differences between Model A and Model B were that Model A was populated with OS, PFS and TTD estimates from the most up to date pooled AURAext/2 dataset whilst Model B was populated with OS, PFS and TTD estimates from the most up to date AURA3 trial data.

During TA416 the company concluded that the most likely utility estimates fell between optimistic values used by the company (derived from data collected during the AURA2 trial) and less optimistic values derived from data collected during the LUME-Lung 1 trial. Health-related quality of life data were collected as part of the AURA3 trial. Utility values derived from these data are very similar to the AURA2 values.

1.2 Summary of exploratory and sensitivity analysis undertaken by the ERG

Following discussion with the NICE technical team, the ERG created a hybrid model (Model A/B) which meets the ToE for this review better than either Model A or Model B. Model A/B has been constructed by replacing the OS, PFS and TTD data in Model A with OS, PFS, TTD data from the AURA3 trial (Model B). Using the CAA price for treatment with osimertinib and list prices for pemetrexed and cisplatin, the ERG has made four amendments to Model A/B, namely revised OS, PFS and TTD estimates (generated using AURA3 trial data) and use of the LUME-Lung 1 trial utility values. The ERG has also presented results from two scenarios:

- Scenario 1: changes to OS, PFS and TTD
- Scenario 2: changes to OS, PFS, TTD and using LUME-Lung 1 trial[1] utility values.

Model A/B base case results and results from these two scenarios are provided in the table below.

Exploratory analyses undertaken by the ERG

ERG amendment/scenario	Incremental			*ICER*	
	Cost	Life years	QALYs	£/QALY	Change from base case
A. Model A/B base case	£68,792	1.030	0.817	£84,209	
Scenario 1: R1)+R2)+R3)	£66,011	1.106	0.897	£73,565	-£10,644
Scenario 2: R1)+R2)+R3)+R4)	£66,011	1.106	0.755	£87,380	£3,171

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

Table 1 Cost effectiveness analysis (Model A/B)

Treatment	Total cost	Total LYG	Total QALYs	Incremental			ICER per QALY gained
				Cost	LYG	QALYs	
Osimertinib*	£92,560	3.082	2.284				
PDC	£23,769	2.052	1.468	£68,792	1.030	0.817	£84,209

ICER=incremental cost effectiveness ratio; LYG=life year gained; PAS=patient access scheme; QALY=quality adjusted life year
* Confidential discounted prices used to estimate the cost of treatment

Table 2 Mean PFS, TTD and OS in Model A/B

Treatment	PFS months (mean)	TTD months (mean)	OS months (mean)
Osimertinib	11.531	[redacted]	36.980
PDC	5.704	[redacted]	24.624

PDC=platinum doublet chemotherapy; PFS=progression-free survival; OS=overall survival; TTD=time to treatment continuation

1.3 Exploratory and sensitivity analyses undertaken by the ERG

1.3.1 Utility values

The utility estimates generated from data collected during the AURA3 trial are very similar to those generated from data collected during the AURA2 trial. The ERG TA416 report[11] includes alternative cost effectiveness results generated using utility values from the LUME-Lung 1 trial[1] (pre-progression=0.67, post-progression=0.64). The NICE AC concluded that the true utility values associated with the pre-progression and post-progression health states are likely to lie somewhere between the estimates from the AURA2 trial and the LUME-Lung 1 trial.[1] The ERG has, therefore, also generated cost effectiveness results using LUME-Lung 1 trial[1] utility values in Model A/B.

Compared with Model A/B base case, this leads to a (0.12) decrease in incremental QALYs (from 0.82 to 0.70) and no change to incremental costs, increasing the ICER per QALY gained for the comparison of osimertinib versus PDC from £84,209 to £98,530.

1.3.2 Survival and treatment costs

For OS, PFS and TTD the company has estimated parametric curves based upon AURA3 trial data. The ERG preferred approach is to use K-M data from trials directly followed by extrapolation of the K-M data after the point at which the K-M data become heavily censored and unreliable. In choosing distributions for extrapolation, cumulative hazard plots of AURA3 trial K-M data for OS, PFS and TTD for osimertinib and PDC were built (cumulative hazard plots are provided in Appendix C). In each case, a constant hazard trend (i.e., a straight line) became evident before the end of the K-M data and so it was appropriate to extrapolate the available K-M data in all cases using exponential functions.

2 IMPACT ON COST EFFECTIVENESS OF ERG ADDITIONAL ANALYSES

A summary of the impact of the ERG's amendments to Model A/B on the cost effectiveness of osimertinib versus PDC for the treatment of patients with advanced or metastatic EGFR T790M mutation-positive disease in the second-line setting after failure of an EGFR-TKI is provided in Table 3.

Using the CAA[2] price for treatment with osimertinib and list prices for pemetrexed and cisplatin, the ERG has made four amendments to Model A/B as detailed in Section 3.2. The ERG presents the results of each amendment individually in Table 3. The ERG also presents the results of two scenarios:

- Scenario 1: changes to OS, PFS and TTD
- Scenario 2: changes to OS, PFS, TTD and using LUME-Lung 1 trial[1] utility values.

Details of all Microsoft Excel revisions carried out by the ERG to Model A/B are presented in Appendix D of this ERG report.

2.1 Conclusions of the cost effectiveness section

The company's submitted ICERs per QALY gained (CDF Review CS, Table 17) ranged from £68,015 to £104,536.

The ERG's hybrid Model A/B yields a base case ICER per QALY gained of £84,209. Compared with PDC, Model A/B base case cost effectiveness results show that treatment with osimertinib generates more QALYs but at an additional cost.

Using Model A/B as the base case, the ERG's revised ICERs per QALY gained range between £73,565 and £98,530. When all of the ERG amendments are combined, the ICER per QALY gained is £87,380.

Table 3 ERG adjustments to Model A/B base case: osimertinib (Commercial Access Agreement price) versus PDC (list prices)

ERG amendment/scenario	Osimertinib			PDC			Incremental			*ICER*	
	Cost	Life years	QALYs	Cost	Life years	QALYs	Cost	Life years	QALYs	£/QALY	Change from base case
A. Model A/B base case	£92,560	3.082	2.284	£23,769	2.052	1.468	£68,792	1.030	0.817	£84,209	
R1) ERG modelling of OS	£91,003	2.808	2.089	£21,348	1.702	1.217	£69,655	1.106	0.871	£79,942	-£4,267
R2) ERG modelling of PFS	£91,130	3.082	2.311	£23,761	2.052	1.468	£67,369	1.030	0.843	£79,925	-£4,284
R3) ERG modelling of TTD	£90,321	3.082	2.284	£24,027	2.052	1.468	£66,295	1.030	0.817	£81,153	-£3,057
R4) LUME-Lung 1 utility values	£92,560	3.082	1.996	£23,769	2.052	1.298	£68,792	1.030	0.698	£98,530	£14,320
Scenario 1: R1)+R2)+R3)	£87,585	2.808	2.115	£21,575	1.702	1.218	£66,011	1.106	0.897	£73,565	-£10,644
Scenario 2: R1)+R2)+R3)+R4)	£87,585	2.808	1.830	£21,575	1.702	1.075	£66,011	1.106	0.755	£87,380	£3,171

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years; TTD=time to treatment discontinuation

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R4) Use ERG suggested utility values	Mod_A	CountryData Add modification to three utility options in this sheet	G680	Use ERG suggested utility value for pre-progression =IF(mod_A=1,0.67,0.833)
			H680	Use ERG suggested utility value for pre-progression =IF(mod_A=1,0.67,0.891)
			I680	Use ERG suggested utility value for pre-progression =IF(mod_A=1,0.67,0.831)
			G681	Use ERG suggested utility value for pre-progression for stable disease also =IF(mod_A=1,0.67,0.753)
			H681	Use ERG suggested utility value for pre-progression for stable disease also =IF(mod_A=1,0.67,0.825)
			I681	Use ERG suggested utility value for pre-progression for stable disease also =IF(mod_A=1,0.67,0.751)
			G682	Use ERG suggested utility value for post-progression =IF(mod_A=1,0.64,((0.751+0.679)/2))
			H682	Use ERG suggested utility value for post-progression =IF(mod_A=1,0.64,0.821)
			I682	Use ERG suggested utility value for post-progression =IF(mod_A=1,0.64,((0.751+0.679)/2))
			G688	Use ERG suggested utility value for pre-progression =IF(Mod_A=1,0.67,0.833)
			H688	Use ERG suggested utility value for pre-progression =IF(Mod_A=1,0.67,0.891)
			I688	Use ERG suggested utility value for pre-progression =IF(Mod_A=1,0.67,0.831)
			G689	Use ERG suggested utility value for pre-progression for stable disease also =IF(Mod_A=1,0.67,0.753)
			H689	Use ERG suggested utility value for pre-progression for stable disease also =IF(Mod_A=1,0.67,0.825)
			I689	Use ERG suggested utility value for pre-progression for stable disease also =IF(Mod_A=1,0.67,0.751)
			G690	Use ERG suggested utility value for post-progression =IF(Mod_A=1,0.0.64,((0.751+0.679)/2))

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
			H690	Use ERG suggested utility value for post-progression =IF(Mod_A=1,0. 0.64,0.821)
			I690	Use ERG suggested utility value for post-progression =IF(Mod_A=1,0. 0.64,((0.751+0.679)/2))
R2) Use ERG re-modelled PFS data from AURA3	Mod_B	ResSurv_B	E22 copy down to E802	Use AURA3 ERG re-modelled PFS for osimertinib =IF(Mod_B=1,'ERG - PFS'!A4,IF(OR(analysis_nr=1,INDEX(surv_model_nr,E$13)=1,SUM(E$17:E$20)=0),0,Survival_func(E$16:E$20,$C22)))
			G22 copy down to G802	Use AURA3 ERG re-modelled PFS for PDC =IF(Mod_B=1,'ERG - PFS'!B4,IF(OR(analysis_nr=1,INDEX(surv_model_nr,G$13)=1,SUM(G$17:G$20)=0),0,Survival_func(G$16:G$20,$C22)))
R1) Use ERG re-modelled OS data from AURA3	Mod_D	ResSurv_B	F22 copy down to F802	Use AURA3 ERG re-modelled OS for osimertinib =IF(Mod_D=1,'ERG - OS'!A3,IF(OR(analysis_nr=1,INDEX(surv_model_nr,F$13)=1,SUM(F$17:F$20)=0),0,CHOOSE(surv_param_model,Survival_func(F$16:F$20,$C22),ClinicalData_B!DV22)))
			H22 copy down to H802	Use AURA3 ERG re-modelled OS for PDC =IF(Mod_D=1,'ERG - OS'!B3,IF(OR(analysis_nr=1,INDEX(surv_model_nr,H$13)=1,SUM(H$17:H$20)=0),0,CHOOSE(surv_param_model,Survival_func(H$16:H$20,$C22),ClinicalData_B!DX22)))
R3) Use ERG re-modelled TTD data from AURA3	Mod_C	PatFlow_B	NB: PDC then OS in this sheet DE13 copy down to DE792	Use AURA3 ERG re-modelled TTD for osimertinib =IF(Mod_C=1,'ERG - TTD'!A3,'AURA3_TTD'!A2)
			DD13 copy down to DD792	Use AURA3 ERG re-modelled TTD for PDC =IF(Mod_C=1,'ERG - TTD'!B3,'AURA3_TTD'!B2)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft technical report

Osimertinib for treating locally advanced or metastatic EGFR T790M mutation positive non-small-cell lung cancer

This document is the draft technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the terms of engagement for the review
- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

Issue date: December 2019

The technical report should be read with the full supporting documents for this appraisal.

1. Topic background

1.1 Appraisal background

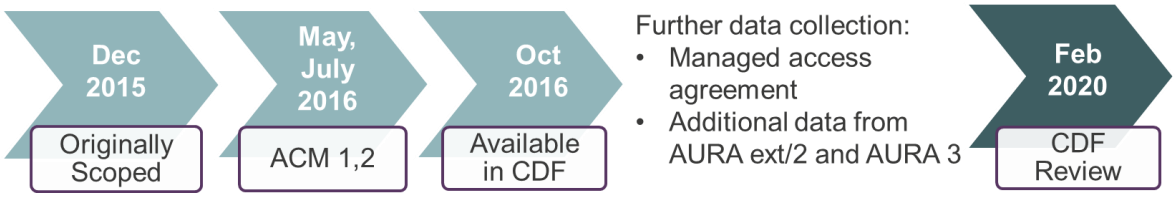
Osimertinib (Tagrisso, AstraZeneca)

NICE TA416: *Osimertinib is recommended as an option for use within the Cancer Drugs Fund (CDF) for treating locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation positive non-small-cell lung cancer (NSCLC) in adults whose disease has progressed only: after first-line treatment with an EGFR tyrosine kinase inhibitor and if the conditions in the managed access agreement for osimertinib are followed.*

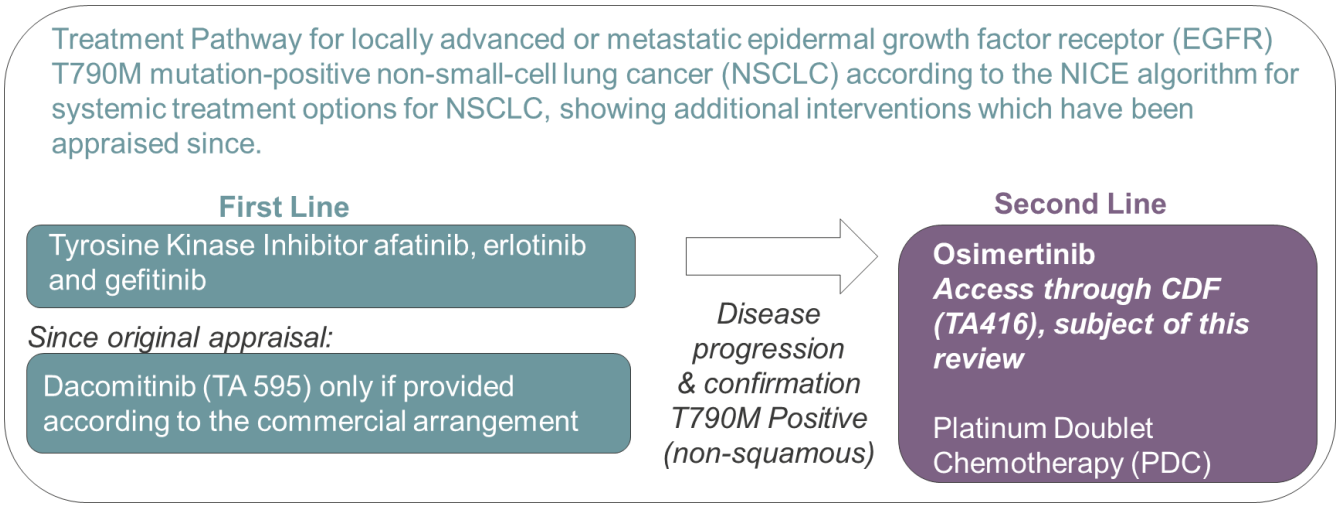
Marketing Authorisation (MA): Osimertinib has a marketing authorisation for 'the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC)'. Recommended dose is 80 mg taken orally once a day until disease progression or unacceptable toxicity.

	Original scope	Original appraisal
Population	People with locally advanced or metastatic, EGFR and T790M mutation positive NSCLC	Restricted to people whose disease has progressed after first line treatment with an EGFR TKI
Comparator (based on population appraised)*	Platinum Doublet Chemotherapy (PDC)	
Outcomes	Overall survival, progression free survival, response rate, adverse treatment effects, health related quality of life	

*Scope included additional comparators for sub-populations not explored in original appraisal; see https://www.nice.org.uk/guidance/ta416/history for more information.



1.2 Treatment pathway



1.3 Key considerations from original appraisal

Committee consideration from original appraisal	Updated information from company for CDF review
Population in scope is adults with locally advanced or metastatic EGFR T790M mutation positive NSCLC. Committee recommendation made in line with evidence (cohort that has progressed on treatment with 1st line EGFR-TKI therapy)	AURA 3 population matches that described in the company Managed Access Agreement and is aligned to population covered by TA416 recommendation
Uncertainty due to lack of direct comparator in clinical trials (to be addressed via ongoing AURA 3 trial in CDF review)	Aura 3 trial compares osimertinib with Platinum Doublet Chemotherapy (PDC)
Immature survival data meant: 1. Could not robustly estimate relative overall survival for osimertinib compared with platinum-doublet chemotherapy (PDC) 2. Uncertain whether osimertinib met End of Life (EoL) Criteria 3. ICER could plausibly fall between £60,663 and £70,776.	Updated OS date from AURAext/2 included in the ARUAext/2 – IMPRESS indirect comparison. New OS data available from AURA 3.
Most plausible utility values fall between 0.67 and 0.831 for response, and 0.67 and 0.751 for stable disease and 0.64 and 0.715 forthe progressed disease state.	Utility values derived from HRoQL data collected for AURA 3 were very similar to AURA 2

1.4 Key clinical evidence

Study	Study type	Treatment	Population	Notes
AURA ext/2 (AURA pooled)	Pooled analysis of 2 single arm studies	Osimertinib	T790M positive advanced NSCLC, progressed after 1st line EGFR TKI	
AURA 3	RCT	Osimertinib, PDC	T790M positive advanced NSCLC, progressed after 1st line EGFR TKI	71% of patients randomised to PDC switched to osimertinib after progression
IMPRESS	Control arm of RCT	PDC	EGFR T790m positive advanced NSCLC who had progressed on 1st line TKI (gefitinib)	Subset of the control arm retrospectively identified as EGFR T790m
IMPRESS/ AURA pooled	Indirect treatment comparison	Osimertinib, PDC	T790M positive advanced NSCLC,	
CDF SACT data	Single arm	Osimertinib	T790M positive advanced NSCLC	
Non-CDF SACT data	Single arm	Any subsequent anti-cancer treatment	Unknown T790M status, subsequent anticancer treatment after initial EGFR TKI	Substantial rates of no subsequent treatment after 1L TKI

1.5 Key trial results: overall survival (OS)

Single-arm studies of osimertinib:

Analysis	Results presented in TA416	Updated results
	Median OS (months) (95% CI)	Median OS (months) (95% CI)
AURAext/2	Not reached	26.3 [24.02 to 29.14] *(DCO5, May 2018)*
CDF SACT	Not applicable	13.9 [12.1-17.6] *(Oct 2016-Jan 2019)*

Comparative analyses of osimertinib:

Analysis	Results presented in TA416		Updated results	
	Median OS (months) (95% CI)	Hazard Ratio (95% CI)	Median OS (months) (95% CI)	Hazard Ratio (95% CI)
AURA3*	Not applicable	----	26.8 [23.49 to 31.54] vs 22.5 ([20.17 to 28.81] (DCO4, March 2019)	0.87 [0.67 to 1.13]
AURAext/2 vs IMPRESS**	Not reached vs 14.1 months	[redacted]		

CDF SACT Data	Treatment	Median OS (95% CI)
	Any 2nd line treatment***	8.31 [7.92 to 11.17]
	No Treatment	2.56 [2.33 to 3.19]

*vs platinum-doublet chemotherapy
**indirect comparison of AURAext/2 and T790M subgroup of IMPRESS placebo arm
***patients with performance status 0/1 who received any subsequent anticancer treatment

1.6 Key trial results: progression-free survival (PFS)

Single-arm studies of osimertinib:

Analysis	Results presented in TA416	Updated results
	Median PFS (months) (95% CI)	Median PFS (months) (95% CI)
AURAext/2	11.0 [9.6 – 12.4]	----
CDF SACT	----	Not available

Comparative analyses of osimertinib:

Analysis	Results presented in TA416		Updated results	
	Median PFS (months) (95% CI)	Hazard Ratio (95% CI)	Median PFS (months) (95% CI)	Hazard Ratio (95% CI)
AURA3*	Not applicable	----	10.1 [8.3 to 12.3] vs. 4.4 [4.2 to 5.3] *(DCO1, April 2016)*	0.3 [0.23 to 4.1]
AURAext/2 vs IMPRESS**	[redacted]			0.251, [0.155 to 0.405]

Non-CDF SACT data (Oct 2016 – Jan 2019):

Treatment	Median PFS (95% CI)
Any 2nd line treatment***	Not available
No Treatment	Not available

*vs platinum-doublet chemotherapy
**indirect comparison of AURAext/2 and T790M subgroup of IMPRESS placebo arm
***patients with performance status 0/1 who received any subsequent anticancer treatment

2. Summary of the draft technical report

2.1 In summary, the technical team considered the following:

Issue 1 The technical team cannot conclude whether the overall survival results from AURA 3 or SACT more accurately reflect clinical reality.

Issue 2 The high proportion of patients crossing over during the AURA 3 trial and limitations of the RPSFTM adjustment method mean there is uncertainty around the overall survival estimates and resulting cost-effectiveness estimates.

Issue 3 The technical team considers the ERG hybrid model to be acceptable (model A/B) as it best meets the Terms of Engagement for the CDF review.

Issue 4 The technical team agrees with the ERG's choice of extrapolating the AURA 3 survival data from the point at which the Kaplan-Meier data becomes heavily censored. Given the technical team's preference for model A/B (see Issue 2), an exponential extrapolation of OS in both treatment arms is reasonable.

Issue 5 The technical team consider that the utility values from the AURA 3 trial support those from AURA2 and IMPRESS, however the technical team remains aware of the uncertainty around the generalisability of these trials to NHS clinical practice. Because of this, the technical team consider that the utility values from the LUME-Lung trial should be considered alongside the AURA2 and IMPRESS utility values.

Issue 6 The point estimates from AURA 3 suggest that the life extension criterium for EoL is met. However, there is substantial uncertainty about the generalisability of these results.

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The Systemic Anti-cancer Therapy (SACT) data collection period was limited (maximum follow period was 28 months)
- The SACT data do not include progression free survival
- The T790M status of patients in the SACT platinum-doublet chemotherapy (PDC) cohort was not known.

2.3 The cost-effectiveness results include a commercial arrangement (patient access scheme) for osimertinib.

2.4 Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) between £73,565 to £87,380 per QALY gained (see Table 1).

2.5 Based on the additional AURA 3 data submitted, it is plausible that the intervention meets the extension to life and therefore meets the end of life criteria (see Issue 6). However, there is substantial uncertainty about the generalisability of the AURA 3 results.

2.6 The technology is considered to be innovative as there have been no treatments specifically for people with EGFR T790M mutation positive NSCLC whose disease is resistant to treatment with TKI agents. The committee concluded that there were no additional benefits associated with this treatment that could not be captured in the economic analysis.

2.7 No equality issues were identified

3. Key issues for consideration

Issue 1 – Differences in overall survival estimates between trials and real world evidence

<table>
<tr><td>Questions for engagement</td><td>1. Do the results of the AURA 3 study reflect the overall survival time seen in clinical practice?
2. What might account for the difference between the AURA trials and CDF/SACT overall survival estimates?</td></tr>
<tr><td>Background/description of issue</td><td><u>TA416 (October 2016):</u>
In the original appraisal, key clinical effectiveness evidence for osimertinib was taken from non-randomised, non-controlled, single arm AURA extension and AURA 2 studies and the clinical effectiveness evidence for platinum doublet chemotherapy came from the IMPRESS study. The committee considered that the available data were too immature to estimate the overall survival gain with osimertinib with any certainty.

<u>CDF Review:</u>
The CDF review includes updated data from AURAext/2 and new data from the AURA 3 trial. In addition, Systemic Anti-Cancer Therapy (SACT) data on osimertinib from the CDF data collection period have been included in the review. A separate SACT dataset collected from patients who had progressed following therapy with an approved EGFR-TKI has been included in the CDF review to provide additional information about patients who were not treated with osimertinib.

Table a: Median OS estimated from different data sources
<table>
<tr><th></th><th colspan="2">Original appraisal</th><th colspan="2">CDF review</th></tr>
<tr><th></th><th>Osimertinib</th><th>PDC</th><th>Osimertinib</th><th>PDC</th></tr>
<tr><td>AURA 3</td><td colspan="2">Not available</td><td>26.8 months</td><td>22.5 months</td></tr>
<tr><td>ITC of AURAext/2 & IMPRESS</td><td>Not reached</td><td>14.1 months</td><td>28.7 months</td><td>14.1 months</td></tr>
</table>
</td></tr>
</table>

SACT data	Not available	13.9 months	8.31 months*

*patients with performance status 0/1 who received any subsequent anticancer therapy

AURA 3 is a randomised, open label trial including 419 patients with EGFR T790M-positive NSCLC, who had disease progression after treatment with first-line EGFR-TKI. Patients randomised to chemotherapy in AURA 3 were permitted to switch treatments after disease progression and 71% of patients crossed over.

The CDF SACT data collected for osimertinib was collected from 386 patients for whom an application for osimertinib was made through the CDF between 4th October 2016 and 4th September 2018. To be eligible patients must have locally advanced or metastatic NSCLC with EGFR and T790M mutation with disease progression following 1st line treatment with an EGFR TKI.

Table b: CDF SACT patient characteristics

Patient characteristics[1]			
		Frequency (N)	**Percentage (%)**
Sex	Male	116	32%
	Female	241	68%
Age	<40	2	1%
	40-49	21	6%
	50-59	79	22%
	60-69	111	31%
	70-79	101	28%
	80+	43	12%
Performance status	0	81	24%
	1	219	61%
	2	21	6%
	3	5	1%
	4	0	0%
	Unknown	31	9%

[1] Figures may not sum to 100% due to rounding.

Median overall survival in AURA 3 was 26.8 months [95% CI: 23.49 to 31.54] for osimertinib compared with 22.5 months [95% CI: 20.17 to 28.81] for PDC (HR 0.87 [95% CI: 0.67 to 1.13]).

An updated analysis of overall survival for the indirect comparison of AURAext/2 and IMPRESS was included in the company submission. Median OS time for osimertinib (AURAext/2) was [redacted] and for PDC (IMPRESS) was 14.1 months.

The overall survival estimate for osimertinib from the pooled AURAext/2 data was 26.3 months [95% CI: 24.02 to 29.14].

From the CDF/SACT data, the median treatment duration for all patients was 9 months [95% CI: 8.3, 10.1] (N=357). Patients receiving treatment at six months was 64% [95% CI: 58%,68%], patients receiving treatment at 12 months was 37% [95% CI: 31%, 43%]. Median survival in 357 patients who received osimertinib was 13.9 months [95% CI: 12.1 to 17.6]

Table c: Time on treatment data for CDF SACT data

Patient status	**Frequency (N)**	**Percentage (%)**
Patient died - on treatment	24	7%
Patient died - not on treatment	156	44%
Treatment stopped	28	8%
Treatment ongoing	149	42%
Total	**357**	

The **company** consider that the availability of mature data from AURAext/2 resolves some of the uncertainty around the survival benefit of patients with a T790M mutation receiving osimertinib after progression on a 1st or 2nd generation TKI. The company consider the survival estimate from the mature data is in agreement with the survival estimate of similar patients in AURA 3.

The **ERG** agree that the survival results from the AURA 3 trial support the findings from the AURAext/2 dataset. The ERG highlight concerns with the crossover adjustment methods (see Issue 2) and the possible impact on the generalisability of the results from the three AURA trials to NHS clinical practice. The ERG considers that whilst patient characteristics and the magnitude of key outcomes from all three AURA trials are similar, the generalisability of this evidence to clinical

	practice is unclear because of differences between trial and Systemic Anti-Cancer Therapy (SACT) dataset survival results, the latter being considerably lower than trial results. The reasons for the large discrepancies are unknown. One possible contributing factor is that the NHS patients were older than those participating in the AURA trials ([redacted]) and, therefore, are unlikely to have received further lines of treatment. **Clinical expert** opinion suggests that an improvement in progression free survival of greater than 3 months would be clinically significant and suggest that without access to line osimertinib, overall survival for this patient group would almost halve. Progression free survival and objective response rate are considered to be the most important outcomes. Clinical expert opinion suggests that real world experience is comparable with trial data. The **technical team** note that although the overall survival estimate from AURA 3 is similar to that of AURA2/ext, it does not show a statistically significant difference in overall survival with osimertinib versus PDC. The technical team also note that survival estimates from the CDF SACT data are considerably lower that from the AURA trials. CDF SACT data is collected in patients who received osimertinib through the CDF following progression after treatment with one TKI (2nd line treatment only). In AURA 3, patients were allowed to switch treatments following progression on PDC (2nd and 3rd line treatment) and in addition, patients were allowed to continue treatment with osimertinib following disease progression if there was judged to be a benefit by the investigator.
Why this issue is important	While the CDF/SACT data does show a survival advantage for osimertinib, it is much lower than reported in the AURA trials and the reason for this is unknown. This increases the uncertainty in the generalisability of the trial results, and in the cost-effectiveness analyses informed by the trial estimates.
Technical team preliminary judgement and rationale	The technical team consider that the results from AURA 3 indicate a potential survival benefit of osimertinib compared with PDC, however note that the results were [redacted]. The SACT data also indicates a survival benefit of osimertinib over PDC; although the overall survival difference was similar, the median overall survival was much lower for both osimertinib and PDC. The technical team cannot conclude whether the results from AURA 3 or SACT more accurately reflect clinical reality.

Issue 2 – Treatment Switching

<table>
<tr><td>Questions for engagement</td><td>1. What is the most appropriate method of adjustment for crossover given the high proportion of patients who switched treatments?
2. How does the high cross-over rate impact the certainty and the generalisability of AURA 3 data?</td></tr>
<tr><td>Background/description of issue</td><td><u>CDF Review (February 2020):</u>
A high proportion (71%) of patients randomised to the PDC arm of the AURA 3 trial switched treatments to osimertinib after disease progression.
The company considered three methods to adjust for switching and determined that the Rank Preserving Structural Failure Time Model (RPSFTM) was the most appropriate method due to the high level of switching in the AURA 3 trial, as the company argue that the RPSFTM method can be used with levels of switching up to 100%. The company generated RPSFTM adjusted OS results using six different approaches (see table).

<table>
<tr><th></th><th>Treatment effect duration</th><th>Re-censoring approach</th><th>Hazard Ratio (95% CI) – Cox Model</th></tr>
<tr><td colspan="3">Base Case</td><td></td></tr>
<tr><td>RPSFTM</td><td>On treatment (osimertinib treatment effect assumed to only occur whilst on treatment)</td><td>Acceleration factor only</td><td>[redacted]</td></tr>
<tr><td colspan="3">Sensitivity Analyses</td><td></td></tr>
<tr><td>RPSFTM</td><td>On treatment (osimertinib treatment effect assumed to only occur whilst on treatment)</td><td>Full (re-censoring applied in the estimation of the acceleration factor and the hazard ratio)</td><td>[redacted]</td></tr>
<tr><td>RPSFTM</td><td>On treatment (osimertinib treatment effect assumed to only occur whilst on treatment)</td><td>None</td><td>[redacted]</td></tr>
</table>
</td></tr>
</table>

	RPSFTM	Treatment group (osimertinib treatment effect assumed to last until death/censoring)	Acceleration factor only	[redacted]
	RPSFTM	Treatment group (osimertinib treatment effect assumed to last until death/censoring)	Full (re-censoring applied in the estimation of the acceleration factor and the hazard ratio)	[redacted]
	RPSFTM	Treatment group (osimertinib treatment effect assumed to last until death/censoring)	None	[redacted]

In the company base case (RPSFTM, on-treatment approach, re-censoring for acceleration factor), the switch-adjusted OS was [redacted]. The company also conducted sensitivity analysis using different treatment effect durations and re-censoring approaches. In all sensitivity analyses, the HR ranged from [redacted]

The **ERG** highlight that the RPSFTM method relies on the assumption that the treatment effect received by switchers is same as that received by patients initially randomised to the experimental arm and suggest this assumption may not be valid when patients only switch after progression. The ERG acknowledge that all crossover adjustment methods are subject to limitations and state they are not aware of a method that would produce a valid estimate of treatment effectiveness when a high proportion of patients crossover at disease progression. The ERG highlight that all RPSFTM scenarios of the RPFSTM generate hazard ratios with [redacted] The ERG consider it is not possible to determine which of the RPSFTM methods generates the most realistic results. The ERG also note that the company's PDC base case median crossover adjusted OS result was more optimistic than results from the company's adjusted indirect comparison or from the SACT data (medians: [redacted]14.1 and 8.31 months respectively).

Why this issue is important	Treatment with osimertinib is not currently recommended or available via the CDF for use after 2nd line therapy. The use of osimertinib in the third line setting is not reflective of NHS practice and the high level of cross-over from following progression on PDC increases the uncertainty in the relative overall survival estimates in the 2nd line indication.

Technical team preliminary judgement and rationale	The high proportion of patients crossing over during the AURA 3 trial and limitations of the RPSFTM adjustment method mean there is uncertainty around the overall survival estimates and resulting cost-effectiveness estimates. The technical team prefer the most cautious approach given the uncertainty and the fact the SACT OS data reflecting NHS practice is much more pessimistic than the trial data.

Issue 3 – Choice of model

<table>
<tr><td>Questions for engagement</td><td>3. Which is the most appropriate model?</td></tr>
<tr><td>Background/description of issue</td><td><u>TA416 (October 2016)</u>
The company model was a cohort based partitioned survival model including 3 health states (progression free disease, progressed disease and death) with a lifetime horizon of 15 years. Data from the AURA extension and AURA 2 were used to estimate progression free survival and overall survival for osimertinib and data from the IMPRESS study was used for platinum doublet chemotherapy.

<u>CDF Review:</u>
The company submitted 2 models. Model A was based on updated OS data from the pooled AURAext/2 data and data from the IMPRESS study (as per TA416). Model B was based on data from AURA 3.
The ERG identified a number of key differences between model A and model B including:
<table>
<tr><td></td><td>Model A</td><td>Model B</td></tr>
<tr><td>Modelling OS</td><td>Weibull extrapolations of AURA pooled and IMPRESS Kaplan-Meier data.</td><td>Log-logistic extrapolation of AURA 3 osimertinib Kaplan-Meier data. This distribution was adjusted by a multiplication factor for the PDC arm.</td></tr>
</table></td></tr>
</table>

Modelling PFS	Gompertz extrapolations of AURA pooled and IMPRESS Kaplan-Meier data.	Weibull extrapolation of AURA 3 osimertinib Kaplan-Meier data. This distribution was adjusted by a multiplication factor for the PDC arm.
Modelling time to treatment discontinuation (TTD)	Osimertinib: AURA2 trial TTD data used directly up to 14.3 months. Estimates 14.3 months to 15 years (model time horizon) were generated using a log-logistic extrapolation. PDC: PFS estimates used up to a maximum of 4 cycles of treatment.	Osimertinib: Generalised gamma distributions were used to estimate TTD for osimertinib and PDC separately.
HRQoL	Utility values used to generate FAD ICERs per QALY gained: PF: 0.831, Stable disease: 0.751, PD: 0.715	Values derived from EQ-5D-5L data (crosswalked to EQ-5D-3L) collected as part of the AURA 3 trial: PF: 0.836, Stable disease: 0.797, PD: 0.717
Resources and costs	Resource use and costs were estimated based on information from the AURAext/2 studies and the IMPRESS trial, published sources and advice from clinical and economic experts.	Resource use and costs were estimated based on information from the AURA 3 study.

Other differences between the two models include:

- differences in the total cost of T790M testing per patient

	• differences in response rates (response rates from AURA2 in Model A and AURA 3 in model B) • differences in adverse event (AE) rates (AURA2 AE rates in Model A and AURA 3 AE rates in model B) and some differences to costs of AEs • differences in resource use items and costs of the items resulting in higher costs in the pre-progression and post-progression health states in Model B and lower costs in Model A for terminal care • small difference to osimertinib administration costs (the higher cost for an initial visit is not included in Model A) • fewer subsequent therapy options in Model B, with an increase in the duration of subsequent therapy for those that are the same as in Model A. The **ERG** considered that the best way of meeting the Terms of Engagement was with a hybrid model (Model A/B), where the model considered in the original appraisal was updated with the new AURA 3 data. The ERG developed this hybrid Model A/B by inserting AURA 3 trial OS, PFS and TTD data (used in Model B) into Model A. The ERG also corrected a minor error in the company's model A (a mid-cycle correction was applied to TTD data; this approach means that, in the first model cycle, not all patients receive their allocated treatment and this leads to an underestimate of the cost of treatment).
Why this issue is important	Company model A generated ICERs per QALY ranging from £68,015 to £79,895 while company model B ICERs ranged from £88,877 to £104,536. The ERG model A/B generated ICERs per QALY between £73,565 and £98,530.
Technical team preliminary judgement and rationale	The technical team considers the hybrid model to be acceptable (model A/B) as it uses the model from TA416 (model A) with new data from AURA 3 (model B) which the technical team agrees meets the terms of engagement.

Issue 4 – Choice of extrapolation to predict overall survival

Questions for engagement	4. What is the most appropriate extrapolation for overall survival?
Background/description of issue	**TA416 (October 2016):** Due to the immaturity of the data, overall survival results were extrapolated from the AURA extension, AURA2 and IMPRESS studies. The company chose a Weibull distribution for both ostimertinib and PDC. The ERG considered the possibility that a generalised gamma distribution might be more appropriate for osimertinib for overall survival but noted that no extrapolation was more valid than any other. Ultimately the committee agreed that due to the immaturity of the data, any estimate of overall survival gain for osimertinib was very uncertain and could have a large effect on the ICER depending on the extrapolation chosen. **CDF Review:** In model A, the **company** extrapolated overall survival using the Weibull distribution for the osimertinib and PDC arms. Choice of extrapolation was based on statistical fit and was in line with the company's approach in the original appraisal. In model B, the company chose the log-logistic distribution to extrapolate both osimertinib and PDC treatment arms. The log-logistic extrapolation was chosen as it provided the best statistical fit and closest estimate to the tail of the data. The company noted that this extrapolation generated the most optimistic OS estimates for PDC in the longer-term. The **ERG** considered the AURA 3 trial to be the most appropriate source from which to estimate the comparative OS of osimertinib versus PDC. The ERG preferred to extrapolate the available Kaplan-Meier data after the point at which the data become heavily censored and unreliable. The ERG considered the cumulative hazard plots of AURA 3 trial Kaplan-Meier data for OS, PFS and TTD for osimertinib and PDC. In each case, a constant hazard trend (i.e. a straight line) became evident before the end of the Kaplan-Meier data and so the ERG chose to extrapolate the available Kaplan-Meier data using exponential functions for the OS, PFS and TTD variables.

Why this issue is important	Immature overall survival data means that there is little certainty of the survival benefit of osimertinib compared with platinum doublet chemotherapy in the long term. This makes it difficult to determine whether introduction of osimertinib is an effective use of NHS resources. Specifically the overall survival estimates have a large impact on the ICERs and may impact on the decision as to whether osimertinib meets the End of Life criteria Overall survival estimates vary greatly depending on the extrapolation chosen and this has a large impact on ICERs. Remodelling OS, PFS and TTD data for osimertinib and PDC using exponential functions results in a reduction in the ICER per QALY gained by £10,644 compared with the company base case when using model A/B.
Technical team preliminary judgement and rationale	The technical team agrees with the extrapolating the AURA 3 survival data from the point at which the Kaplan-Meier data becomes heavily censored. Given the technical team's preference for model A/B (see Issue 2), an exponential extrapolation of OS in both treatment arms is reasonable.

Issue 5 – Choice of utility values

Questions for engagement	5. What are the most appropriate utility values?
Background/description of issue	**TA416 (October 2016):** In the company's model (2nd line only), utility values for progression-free disease were based on the IMPRESS study (0.831 for treatment response, 0.751 for stable disease for both treatments). The model assumed a utility value of 0.715 for progressed disease (based on a midpoint between the AURA EQ-5D-5L crosswalk value and the IMPRESS EQ-5D-3L value). The ERG considered the utility values from the LUME-lung 1 study could be more reasonable (0.67 utility value for both the response and stable states and 0.64 for the progressed disease state). This was because the ERG considered the company values to be implausibly high for patients with metastatic NSCLC whose disease has progressed after first line TKI therapy. The committee concluded that the most plausible utility values would fall somewhere between those used by the company in its updated analysis and those suggested by the ERG. The committee considered the importance of incorporating response rates as an improved response rate with osimertinib compared with PDC could result in improvements in quality of life and therefore

	utility. The committee conclude the benefits of improving overall response rates had a minor effect on the company's cost effectiveness results. **CDF Review:** The **company** submitted two separate models. Model A used utilities sourced from AURA 2 and IMPRESS as in the original TA416. The company did a sensitivity analysis using the ERG preferred utilities from TA416. However the company considered that there were a number of issues with the alternate utility values in the LUME-LUNG 1 study, including concerns that the values are derived from a different patient population who were not previously treated with an EGFR-TKI and in whom T790M mutation status was unknown, concerns that patients in the LUME-LUNG 1 trial were treated with cytotoxic chemotherapy, and that the values do not account for response rates. In model B, the company used utility values derived from AURA 3 (PFS: 0.836, SD: 0.797, PD: 0.717, Death: 0) and again explored the ERG preferred values in a sensitivity analysis. The **ERG** has used the same utility values in their base case as those used by the company in TA416 and also generated cost effectiveness results using utility values from the LUME-Lung Trial for comparison. Using the LUME-Lung Trial values results in a 0.12 decrease in incremental QALYs, increasing the ICER per QALY gained from £84,209 to £98,530. The ERG noted that the utility values from AURA 3 are very similar to those generated from data collected during AURA2. **Patient Organisation** feedback suggests that "quality of life is significantly improved on osimertinib, both in terms of side effects and time spent at hospital appointments or receiving treatment for side effects" and support the clinical expert opinion about ease of administration and tolerance for patients.
Why this issue is important	In model A the base case ICER was £68,015 compared with £79,895 when using the ERG preferred utilities. In model B, using the company preferred values, the ICER is £88,877 compared with £104,536 when using the ERG preferred utilities.

	In model A/B using the company preferred utilities, the ICER is £84,209 but using the LUME-LUNG 1 values increases the ICER to £98,530 All ERG combined changes in the model result in an ICER of £87,380.
Technical team preliminary judgement and rationale	The technical team consider that the utility values from the AURA 3 trial support those from AURA2 and IMPRESS. However the technical team remains aware of the uncertainty around generalisable the results of these trials are to NHS clinical practice (see Issue 1). Because of this, the technical team consider that the utility values from the LUME-Lung trial should be considered alongside the AURA2 and IMPRESS utility values.

Issue 6 – End of Life Criteria

Questions for engagement	1. Does osimertinib meet the extension to life criteria?
Background/description of issue	**TA416 (October 2016):** In the original appraisal, the committee concluded that people for whom osimertinib is indicated have a short life expectancy and that it was reasonable to conclude that there was likely to be an overall survival gain for osimertinib of over 3 months. Based on the evidence available at the time of original assessment the committee therefore considered it plausible that osimertinib met the criteria to be considered a life extending, end-of-life treatment. The Terms of Engagement state that this should be reconsidered when more data from the AURA studies, including AURA 3 became available. **CDF Review:** Point estimates from both AURA 3 and updated indirect comparison of AURAext/2 and IMPRESS indicate an overall survival gain of more than 3 months for osimertinib compared with PDC. The **company** did not specifically discuss end of life criteria in their submission. However Table 9 of the company submission (comparing AURA 3 crossover adjusted median OS results) indicates that the minimum OS gain with osimertinib compared to PDC would be [redacted] and the maximum would be [redacted].

	The company modelling of AURA 3 data give a mean OS of 36.9 months for osimertinib versus 24.6 months for PDC. The **ERG** revised mean estimates of OS are 33.7 months and 20.4 months respectively. The ERG concluded that the life extension criteria are met. However, the **technical team** note the uncertainty around the generalisability of the AURA 3 and AURAext/2 results due to the difference in survival estimates compared to the SACT data (see Issue 1) **The patient organisation** considers that the survival benefit and improved quality of life offered by osimertinib cannot be underestimated.
Why this issue is important	If the end of life criteria are met, it may be appropriate to recommend a treatment that has an ICER that exceeds the upper end of the range normally approved by the Appraisal Committee.
Technical team preliminary judgement and rationale	The point estimates from AURA 3 suggest that the life extension criteria are met, but there is substantial uncertainty about the generalisability and robustness of the trial estimates (see Issues 1 and 2).

5. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided. All estimates take account of the commercial arrangements for osimertinib.

Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate

Alteration	Technical team rationale	ICER	Change from base case
Company Model A (base case)		**£68,015**	
Company Model B		**£88,877**	
1) ERG hybrid model A/B using AURA 3 data for OS, PFS and TTD	Technical team agreed with ERG's assessment that a hybrid model best meets the Terms of Engagement (see Issue 2)	£84,209	+£16,194
2) Use of exponential functions for extrapolation of AURA 3 OS, PFS and TTD data.	Technical team agreed with ERG's use of exponential functions (see Issue 3)	£73,565	+£5,550
3) Use of utility values derived from LUME-Lung 1 trial in Model A/B	Technical team consider utility values from LUME-Lung 1 study should be considered alongside utility values from AURA2 and IMPRESS (see Issue 5)	£98,530	+£30,515
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	**£73,565 to £87,380**	**+£5,550 to £19,365**

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Comments
Stopping rule	The marketing authorisation states that treatment should continue until disease progression or unacceptable toxicity. AURA 3 criteria state that patients were allowed to receive trial treatment beyond the point of disease progression as long as they were receiving clinical benefit as judged by the investigator. It is unclear how many patients this applied to and this adds to the uncertainty around the generalisability of AURA 3. However, the technical team note that the trial protocol for treatment discontinuation appears to be in line with clinical practice in the NHS.

Table 3: Other issues for information

Issue	Comments
Progression-free survival	Progression free survival in AURA 3 is 10.1 [95% CI: 8.3 to 12.3] vs. 4.4 [95% CI 4.2 to 5.3], HR=0.3 [95% CI, 0.23 to 4.1]. Progression free survival data were not available from the CDF/SACT data No updated PFS analysis was provided for AURAext/2 vs IMPRESS indirect treatment comparison.
Time to treatment discontinuation	Time to treatment discontinuation (TTD) was included appropriately in TA416 In company model A, TTD for Osimertinib AURA2 trial used directly up to 14.3 months. Estimates 14.3 months to 15 years (model time horizon) were generated using a log-logistic extrapolation. For PDC, PFS estimates used up to a maximum of 4 cycles of treatment. In company model B generalised gamma distributions were used to estimate TTD for osimertinib and PDC separately The ERG used model A/B and extrapolated TTD using an exponential function.
Innovation	In TA416, the committee concluded that osimertinib is innovative because there have been no treatments specifically for people with EGFR T790M mutation positive NSCLC whose disease is resistant to treatment with TKI agents, and that there was an unmet need for people with this condition. However, the committee concluded that there were no additional benefits associated with this treatment that could not be captured in the economic analysis.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

Authors

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer (CDF Review of TA416) [ID1577]

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**AstraZenecaUK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Data are too immature to robustly estimate overall survival advantage of osimertinib compared with platinum doublet chemotherapy	
Does the additional data submitted improve certainty of overall survival estimates?	PFS results from the MAIC of AURA2/ext and IMPRESS (HR 0.251 [0.155 – 0.405]) and AURA3 (HR 0.3 [0.23 – 0.41]) are similar and demonstrate the reproducibility of the efficacy of osimertinib in delaying progression in patients. Estimates of median OS are similarly consistent across studies (approximately 26.8 [AURA3] – 28.7 [AURA2 MAIC] months for osimertinib, compared to 14.1 [IMPRESS MAIC] – 15.9 [base case RPSFTM for AURA3] months for PDC). In terms of relative efficacy, the adjusted OS hazard ratios for both studies are also consistent: AURA2/ext – IMPRESS MAIC = 0.514 (0.323 – 0.816), AURA3 RPSFTM = 0.54 (0.18 – 1.60). These results suggest that clinical outcomes of AURA3 and AURA2/ext are aligned and reproducible in a clinical trial setting.
Is it possible the results of the AURA3 study over-estimate the survival advantage of osimertinib compared with what is seen in clinical practice?	It is possible that the OS results of the AURA3 study represent an over-estimate of the life expectancy of patients receiving osimertinib or PDC compared with current standard NHS practice.

	It is however, important to recognise that the median time on treatment for patients receiving osimertinib in both trial settings and whilst available in the CDF are very similar.
What might account for the difference between the AURA trials and CDF/SACT overall survival estimates?	As discussed at the technical review meeting (as well as in a number of appraisal meetings), the fitness of patients in the NHS is less than that of patients recruited to clinical trials and therefore expected to have a poorer prognosis. Indeed, the clinical expert at the technical review meeting suggested that delays in identifying patients as eligible for osimertinib treatment mean that significant growth of the cancer has occurred before treatment has started, often manifesting itself in poorer fitness in general. Given the observation outlined in the previous response, i.e. that patients in both CDF and trial settings had similar levels of exposure to osimertinib, it is likely that differences in post-progression care may explain some of the disparities between overall survival estimates. It is known from available evidence, that patients with EGFRm NSCLC are unlikely to receive more than 2 or 3 lines of therapy (i.e. 1 line of therapy after osimertinib or PDC), whereas patients in clinical trials often have multiple lines of therapies after the controlled phase of a study.
Issue 2: End of Life Criteria	
Does osimertinib meet the criteria for end-of life treatment?	Yes. There is almost universal agreement that the life expectancy of patients with EGFRm advanced NSCLC who have progressed following treatment with an EGFRm TKI (erlotinib, gefitinib or afatinib) is less than 24 months. Furthermore, there is little doubt (from the original submission, the revised models produced by the ERG and clinician and patient statements) that

	the survival benefit of osimertinib in those patients with T790M resistance mutation is likely to be considerably more than 3 months.
Issue 3: Choice of extrapolation to predict overall survival greatly impacts ICER estimates	
What is the most appropriate extrapolation for overall survival?	It is reasonable to use an exponential extrapolation for OS in both arms of the cost-effectiveness model.
Issue 4: Choice of utility values	
What are the most appropriate utility values?	AstraZeneca believe that the health state utility values obtained from the AURA3 study are the most relevant source of utility values for the population being considered in this appraisal, that is, patients with EGFR T790M mutation-positive locally advanced or metastatic NSCLC. This study produced utility values of 0.831 for the progression-free state and 0.715 for the progressed state based on data from the original submission. The ERG argue in their report that the previous appraisal of osimertinib for the treatment of patients with EGFR T790M mutation-positive locally advanced or metastatic NSCLC concluded that the most plausible utility values would most likely fall between those used by the company (AURA 2 - 0.815 for progression-free disease and 0.678 for post-progression disease) and those suggested by the ERG (LUME-Lung 1 - 0.67 for progression-free disease and 0.64 for the progressed disease state). Given the similarity of the utility values given by both the AURA2 and AURA3 studies, AstraZeneca consider these results to be confirmatory in nature and therefore indicative that the most plausible utility values are those observed in the trials.

	Further to this, when considering patient and clinician feedback there has been clear suggestion that osimertinib significantly improves quality of life when compared to standard of care, and therefore the fact that utilities have been modelled as health state, rather than treatment specific may bias the results of a cost effectiveness analysis against osimertinib. Given the source of the utility values preferred by the ERG is the LUME-Lung 1 study, where all patients received docetaxel as chemotherapy (with or without nintedanib), AstraZeneca considers this data source to be more aligned to the experience of patients receiving PDC in this appraisal. In order to address this AstraZeneca has run a number of scenarios to estimate the ICER in relation to the ERG base case range, this is shown in the table provided in the supporting document.
Issue 5: Treatment Switching	
Given the high proportion of patients crossing over in AURA3, is it appropriate to adjust for treatment switching?	Given the high level of crossover in AURA3, and the current restriction of osimerinib use in the NHS to patients who have only received one line of therapy before starting osimertinib (i.e. a second-line treatment option only), it is entirely appropriate to adjust for the effect of patients randomised to PDC in AURA3 receiving osimertinib as a third-line treatment. It is, however acknowledged that the reliability of standard adjustment methods in this case is unclear and therefore all estimates of efficacy within the confines of the appraisal must be interpreted with caution.

	We note that during the technical review meeting the ERG could not suggest a better method to adjust for crossover and said that the method used in the submission was “the most reasonable”.
If not appropriate, how does this impact the generalisability of AURA3?	The response to Issue 1 is relevant here. The close alignment of PFS and OS results for AURA2/ext and AURA3 supports an argument for the reproducibility and robustness of the efficacy of osimertinib in a clinical trial setting.

Supplementary material.

In order to address the uncertainty around the most appropriate utility values for patients eligible for treatment with osimertinib, AstraZeneca has run a number of scenarios in relation to the ERG base case model which reflect the arguments provided in the main technical engagement response document.

Scenario	ICER
ERG Base Case (Health state utilities, LUME-Lung 1)	£87,380
ERG Base Case (Health State utilities, AURA3)	£73,565
Scenario 1: Health State utilities, Midpoint between LUME-Lung 1 and AURA 3 (Scenario 1 in the Settings sheet, Response = 0.751, Stable disease = 0.711, Progressed disease = 0.678)	£79,880
Scenario 2: Treatment specific utilities, PDC = LUME-Lung 1, (Response = 0.67, Stable disease = 0.67, Progressed disease = 0.64) Osimertinib = Midpoint between LUME-Lung 1 and AURA 3 (Response = 0.751, Stable disease = 0.711, Progressed disease = 0.678) (Scenario 2 in the Settings sheet)	£73,496
Scenario 3: Treatment specific utilities, PDC = LUME-Lung 1, (Response = 0.67, Stable disease = 0.67, Progressed disease = 0.64) Osimertinib = AURA 3 (Response = 0.831, Stable disease = 0.751, Progressed disease = 0.715) (Scenario 3 in the Settings sheet)	£63,419

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About you

Your name	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NCRI-ACP-RCP-RCR**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Data are too immature to robustly estimate overall survival advantage of osimertinib compared with platinum doublet chemotherapy	
Does the additional data submitted improve certainty of overall survival estimates?	Yes – the updated AURAext/2 and AURA3 results improves certainty of expected OS estimates
Is it possible the results of the AURA3 study over-estimate the survival advantage of osimertinib compared with what is seen in clinical practice?	Yes – potentially, as outcomes in all selected study population may not be generalizable to the broader clinical population and there is a risk the OS advantages are over-estimated and we do note that the SACT PDC group is not identical to the AURA3 PDC arm. Conversely SACT is unlikely to collect data of a comparable quality to trial data so reliance on SACT data for survival estimates also has its potential bias.
What might account for the difference between the AURA trials and CDF/SACT overall survival estimates?	The real world data will be collected from a more heterogeneous population where many clinical prognostic factors will have not been stratified / controlled as happens in the clinical trial setting eg differences in age, gender, ethnicity, performance status, burden of disease (including % with CNS metastases), co-morbidities, etc. Individually each of these factors could affect survival outcomes and caution must be applied when comparing outcomes from a carefully selected study population with real world data.
Issue 2: End of Life Criteria	
Does osimertinib meet the criteria for end-of life treatment?	Yes
Issue 3: Choice of extrapolation to predict overall survival greatly impacts ICER estimates	
What is the most appropriate extrapolation for overall survival?	

Issue 4: Choice of utility values	
What are the most appropriate utility values?	
Issue 5: Treatment Switching	
Given the high proportion of patients crossing over in AURA3, is it appropriate to adjust for treatment switching?	Yes - cross over needs to be considered in interpreting the survival data.
If not appropriate, how does this impact the generalisability of AURA3?	

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About you

Your name	**Kevin Lock**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**AstraZenecaUK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

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ERG response	The ERG agrees with the company that the PFS results from the AURA3 trial support the PFS results from the AURA2/ext and IMPRESS MAIC. However, the ERG highlights that the PDC median OS estimates from the AURA3 trial, after adjusting for crossover, range from [redacted] to [redacted] and [redacted] median OS PDC estimates from the AURA3 trial are similar to the median OS PDC estimate from the MAIC of AURA2/ext and the IMPRESS trial.

	In addition, when comparing the adjusted OS hazard ratios, from the MAIC of AURA2/ext and the IMPRESS trial and the AURA 3 trial (RPFSTM base case), it is difficult to ignore the very wide confidence interval around the AURA3 trial OS hazard ratio.
Is it possible the results of the AURA3 study over-estimate the survival advantage of osimertinib compared with what is seen in clinical practice?	It is possible that the OS results of the AURA3 study represent an over-estimate of the life expectancy of patients receiving osimertinib or PDC compared with current standard NHS practice. It is however, important to recognise that the median time on treatment for patients receiving osimertinib in both trial settings and whilst available in the CDF are very similar.
ERG response	The ERG agrees with the company.
What might account for the difference between the AURA trials and CDF/SACT overall survival estimates?	As discussed at the technical review meeting (as well as in a number of appraisal meetings), the fitness of patients in the NHS is less than that of patients recruited to clinical trials and therefore expected to have a poorer prognosis. Indeed, the clinical expert at the technical review meeting suggested that delays in identifying patients as eligible for osimertinib treatment mean that significant growth of the cancer has occurred before treatment has started, often manifesting itself in poorer fitness in general. Given the observation outlined in the previous response, i.e. that patients in both CDF and trial settings had similar levels of exposure to osimertinib, it is likely that differences in post-progression care may explain some of the disparities between overall survival estimates. It is known from available evidence, that patients with EGFRm NSCLC are unlikely to receive more

	than 2 or 3 lines of therapy (i.e. 1 line of therapy after osimertinib or PDC), whereas patients in clinical trials often have multiple lines of therapies after the controlled phase of a study.
ERG response	The ERG agrees with the company.
Issue 2: End of Life Criteria	
Does osimertinib meet the criteria for end-of life treatment?	Yes. There is almost universal agreement that the life expectancy of patients with EGFRm advanced NSCLC who have progressed following treatment with an EGFRm TKI (erlotinib, gefitinib or afatinib) is less than 24 months. Furthermore, there is little doubt (from the original submission, the revised models produced by the ERG and clinician and patient statements) that the survival benefit of osimertinib in those patients with T790M resistance mutation is likely to be considerably more than 3 months.
ERG response	The ERG considers that treatment with osimertinib meets both the short life expectancy and the life extension criteria.
Issue 3: Choice of extrapolation to predict overall survival greatly impacts ICER estimates	
What is the most appropriate extrapolation for overall survival?	It is reasonable to use an exponential extrapolation for OS in both arms of the cost-effectiveness model.
ERG response	The ERG has no further comment.
Issue 4: Choice of utility values	

What are the most appropriate utility values?	AstraZeneca believe that the health state utility values obtained from the AURA3 study are the most relevant source of utility values for the population being considered in this appraisal, that is, patients with EGFR T790M mutation-positive locally advanced or metastatic NSCLC. This study produced utility values of 0.831 for the progression-free state and 0.715 for the progressed state based on data from the original submission. The ERG argue in their report that the previous appraisal of osimertinib for the treatment of patients with EGFR T790M mutation-positive locally advanced or metastatic NSCLC concluded that the most plausible utility values would most likely fall between those used by the company (AURA 2 - 0.815 for progression-free disease and 0.678 for post-progression disease) and those suggested by the ERG (LUME-Lung 1 - 0.67 for progression-free disease and 0.64 for the progressed disease state). Given the similarity of the utility values given by both the AURA2 and AURA3 studies, AstraZeneca consider these results to be confirmatory in nature and therefore indicative that the most plausible utility values are those observed in the trials. Further to this, when considering patient and clinician feedback there has been clear suggestion that osimertinib significantly improves quality of life when compared to standard of care, and therefore the fact that utilities have been modelled as health state, rather than treatment specific may bias the results of a cost effectiveness analysis against osimertinib. Given the source of the utility values preferred by the ERG is the LUME-Lung 1 study, where all patients received docetaxel as chemotherapy (with or without nintedanib), AstraZeneca considers this data source to be more aligned to the experience of patients receiving PDC in this appraisal.

	In order to address this AstraZeneca has run a number of scenarios to estimate the ICER in relation to the ERG base case range, this is shown in the table provided in the supporting document.
ERG response	Prior to osimertinib entering the CDF, the NICE AC concluded that the true utility values associated with the pre-progression and post-progression health states were likely to lie somewhere between the estimates from the AURA2 trial and the LUME-Lung 1 trial. The estimates from the AURA3 trial are similar to those from the AURA2 trial. The ERG has been unable to find any utility estimates, that have been published since the original appraisal, that are relevant to patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC. The ERG has been able to replicate the ICER per QALY gained generated by the additional scenarios presented in the supporting document supplied by the company. The ERG highlights that the AURA3 utility values used in these scenarios differ to those used in the company model B base case analysis (CDF Review CS).
Issue 5: Treatment Switching	
Given the high proportion of patients crossing over in AURA3, is it appropriate to adjust for treatment switching?	Given the high level of crossover in AURA3, and the current restriction of osimerinib use in the NHS to patients who have only received one line of therapy before starting osimertinib (i.e. a second-line treatment option only), it is entirely appropriate to adjust for the effect of patients randomised to PDC in AURA3 receiving osimertinib as a third-line treatment. It is, however acknowledged that the reliability of standard adjustment methods in this case is unclear and

	therefore all estimates of efficacy within the confines of the appraisal must be interpreted with caution. We note that during the technical review meeting the ERG could not suggest a better method to adjust for crossover and said that the method used in the submission was “the most reasonable”.
ERG response	The ERG considers that, due to the high level of crossover in the AURA3 trial, adjusting for crossover is appropriate but highlights that all crossover adjustment methods have limitations. For this appraisal, the ERG considers that it is not possible to choose a ‘best’ method of crossover adjustment; furthermore, choosing the most appropriate of the six variants of the RPFSTM method is also not possible.
If not appropriate, how does this impact the generalisability of AURA3?	The response to Issue 1 is relevant here. The close alignment of PFS and OS results for AURA2/ext and AURA3 supports an argument for the reproducibility and robustness of the efficacy of osimertinib in a clinical trial setting.
ERG response	Despite the highlighted uncertainties, the ERG considers that the AURA3 trial is the best source of evidence for the comparison of the relative efficacy of treatment with osimertinib versus PDC in a population of adults with locally advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease has progressed following treatment with an EGFR TKI.

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Professor Gary McVeigh

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Piccadilly Plaza,

Manchester,

M1 4BT

3rd August 2020

CONFIDENTIAL

Dear Professor McVeigh,

With reference to Osimertinib for the CDF review of NICE TA 416 (ID1577)

Following the first Appraisal Committee meeting held on 6th February 2020, AstraZeneca has increased the confidential discount for osimertinib from [redacted]% to [redacted]% on the current list price of £5,770 per 30-tablet pack (confidential net price from £[redacted] to £[redacted]).

When populating the economic model with the assumptions in the company base case

(Treatment specific utilities, PDC = LUME-Lung 1, Osimertinib = AURA 3) the ICER reduces from £[redacted] to £36,034, with the new discount. In the requested scenario analyses, the ICERs at the updated discount change as follows:

Scenario based on health state utility values from AURA2 - £[redacted] to £41,799

Scenario based on the LUME Lung 1 utility values - £[redacted] to £49,649

Thereby, demonstrating cost-effectiveness in all scenarios, given the end of life criteria are met.

We thank you for your assistance with this submission and are happy to discuss this further with

you as required.

Your sincerely,

[redacted]